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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  FEB 28  PATDPAFULL - New display fields provide for legal status
                  data from INPADOC
 NEWS  4  FEB 28  BABS - Current-awareness alerts (SDIs) available
 NEWS  5  MAR 02  GBFULL: New full-text patent database on STN
 NEWS  6  MAR 03  REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 22  KOREAPAT now updated monthly; patent information enhanced
 NEWS  9  MAR 22  Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS  10 MAR 22  PATDPASPC - New patent database available
 NEWS  11 MAR 22  REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS  12 APR 04  EPFULL enhanced with additional patent information and new
                  fields
 NEWS  13 APR 04  EMBASE - Database reloaded and enhanced
 NEWS  14 APR 18  New CAS Information Use Policies available online
 NEWS  15 APR 25  Patent searching, including current-awareness alerts (SDIs),
                  based on application date in CA/CAplus and USPATFULL/USPAT2
                  may be affected by a change in filing date for U.S.
                  applications.
 NEWS  16 APR 28  Improved searching of U.S. Patent Classifications for
                  U.S. patent records in CA/CAplus
 NEWS  17 MAY 23  GBFULL enhanced with patent drawing images
 NEWS  18 MAY 23  REGISTRY has been enhanced with source information from
                  CHEMCATS
 NEWS  19 JUN 06  The Analysis Edition of STN Express with Discover!
                  (Version 8.0 for Windows) now available
 NEWS  20 JUN 13  RUSSIAPAT: New full-text patent database on STN
 NEWS  21 JUN 13  FRFULL enhanced with patent drawing images
 NEWS  22 JUN 27  MARPAT displays enhanced with expanded G-group definitions
                  and text labels
 NEWS  23 JUL 01  MEDICONF removed from STN
 NEWS  24 JUL 07  STN Patent Forums to be held in July 2005
 NEWS  25 JUL 13  SCISEARCH reloaded
 NEWS  26 JUL 20  Powerful new interactive analysis and visualization software,
                  STN AnaVist, now available

 NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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 NEWS WWW      CAS World Wide Web Site (general information)

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*ENCOMPPAT     - EnCompass Patent File 1964-present (Supporters)
*ENCOMPPAT2    - EnCompass Patent File 1964-Present (Non-Supporters)

  * The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005

=> file medline
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

 FILE LAST UPDATED: 23 JUL 2005 (20050723/UP).  FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available.  For details enter HELP
 RLOAD at an arrow promt (=>).  See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s WNT
          3897 WNT
           336 WNTS
L1        3942 WNT
               (WNT OR WNTS)

=> s l1 (S) antagon?
        518406 ANTAGON?
L2         244 L1 (S) ANTAGON?

=> s osteo? or bone
        211167 OSTEO?
        424243 BONE
         91740 BONES
        446342 BONE
               (BONE OR BONES)
L3      553450 OSTEO? OR BONE

=> s l3 and l2
L4          70 L3 AND L2

=> s multiple myeloma
        445180 MULTIPLE
```

```
          3940 MULTIPLES
        446855 MULTIPLE
                 (MULTIPLE OR MULTIPLES)
         30767 MYELOMA
           763 MYELOMAS
         31029 MYELOMA
                 (MYELOMA OR MYELOMAS)
L5       22597 MULTIPLE MYELOMA
                 (MULTIPLE(W)MYELOMA)

=> s l5 and l4
L6           1 L5 AND L4

=> d ibib 1

L6   ANSWER 1 OF 1     MEDLINE on STN
ACCESSION NUMBER:    2003612654     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 14695408
TITLE:               The role of the Wnt-signaling antagonist
                     DKK1 in the development of osteolytic lesions in
                     multiple myeloma.
COMMENT:             Comment in: N Engl J Med. 2003 Dec 25;349(26):2479-80.
                     PubMed ID: 14695406
                     Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                     reply 1464-6. PubMed ID: 15070800
                     Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                     reply 1464-6. PubMed ID: 15074002
                     Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                     reply 1464-6. PubMed ID: 15074001
                     Comment in: N Engl J Med. 2004 Jul 8;351(2):197-8. PubMed
                     ID: 15247367
AUTHOR:              Tian Erming; Zhan Fenghuang; Walker Ronald; Rasmussen Erik;
                     Ma Yupo; Barlogie Bart; Shaughnessy John D Jr
CORPORATE SOURCE:    Donna D. and Donald M. Lambert Laboratory of Myeloma
                     Genetics, Myeloma Institute for Research and Therapy,
                     College of Medicine, University of Arkansas for Medical
                     Sciences, Little Rock 72205, USA.
CONTRACT NUMBER:     CA55819 (NCI)
     CA97513 (NCI)
SOURCE:              New England journal of medicine, (2003 Dec 25) 349 (26)
                     2483-94.
                     Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200401
ENTRY DATE:          Entered STN: 20031230
                     Last Updated on STN: 20040107
                     Entered Medline: 20040106


=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1           3942 S WNT
L2            244 S L1 (S) ANTAGON?
L3         553450 S OSTEO? OR BONE
L4             70 S L3 AND L2
L5          22597 S MULTIPLE MYELOMA
L6              1 S L5 AND L4

=> s l2 and l5
```

```
L7            1 L2 AND L5

=> s myeloma
         30767 MYELOMA
           763 MYELOMAS
L8       31029 MYELOMA
                (MYELOMA OR MYELOMAS)

=> s l8 and l2
L9            1 L8 AND L2

=> s l1 and l3
L10         451 L1 AND L3

=> s l10 and l5
L11           7 L10 AND L5

=> s l11 not py>2002
       1489868 PY>2002
L12           1 L11 NOT PY>2002

=> d ibib

L12  ANSWER 1 OF 1     MEDLINE on STN
ACCESSION NUMBER:   2001420323     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11468178
TITLE:              Identifying intercellular signaling genes expressed in
                    malignant plasma cells by using complementary DNA arrays.
AUTHOR:             De Vos J; Couderc G; Tarte K; Jourdan M; Requirand G;
                    Delteil M C; Rossi J F; Mechti N; Klein B
CORPORATE SOURCE:   INSERM U475, Unit for Cellular Therapy, CHU Montpellier, 99
                    Rue Puech Villa, 34197 Montpellier Cedex 5, France.
SOURCE:             Blood, (2001 Aug 1) 98 (3) 771-80.
                    Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200109
ENTRY DATE:         Entered STN: 20010917
                    Last Updated on STN: 20010917
                    Entered Medline: 20010913


=> d kwic

L12  ANSWER 1 OF 1     MEDLINE on STN
AB   In multiple myeloma (MM), the growth of primary plasma
     cells depends not only on interleukin-6 (IL-6), but also on additional
     unidentified signals delivered by the bone marrow environment.
     Using Atlas complementary DNA (cDNA) arrays comprising 268 genes coding
     for intercellular signaling molecules, this study identified genes.  .  .
     receptor (TR) that is linked to HB-EGF and syndecan-1 processing and to
     cell invasion, chemokine receptors CCR1 and CCR2, the Wnt
     pathway actor Frizzled-related protein (FRZB), and the Notch receptor
     ligand Jagged 2.  These data, obtained with the Atlas cDNA array,.  .  .
CT    B-Lymphocytes: ME, metabolism
      Cell Division: DE, drug effects
      Epidermal Growth Factor: ME, metabolism
      Flow Cytometry
      Gene Expression: GE, genetics
      Humans
        Multiple Myeloma: GE, genetics
       *Multiple Myeloma: ME, metabolism
        Multiple Myeloma: PA, pathology
```

```
      Neoplasm Proteins: GE, genetics
      Neoplasm Proteins: ME, metabolism
     *Oligonucleotide Array Sequence Analysis: MT, methods
     *Plasma Cells:.  .  .


=> s (dickkopf () 1) or (DKK () 1)
            85 DICKKOPF
             8 DICKKOPFS
            90 DICKKOPF
                 (DICKKOPF OR DICKKOPFS)
       3513889 1
            49 DICKKOPF (W) 1
           119 DKK
             9 DKKS
           121 DKK
                 (DKK OR DKKS)
       3513889 1
            44 DKK (W) 1
L13         70 (DICKKOPF (W) 1) OR (DKK (W) 1)

=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1        3942 S WNT
L2         244 S L1 (S) ANTAGON?
L3      553450 S OSTEO? OR BONE
L4          70 S L3 AND L2
L5       22597 S MULTIPLE MYELOMA
L6           1 S L5 AND L4
L7           1 S L2 AND L5
L8       31029 S MYELOMA
L9           1 S L8 AND L2
L10        451 S L1 AND L3
L11          7 S L10 AND L5
L12          1 S L11 NOT PY>2002
L13         70 S (DICKKOPF () 1) OR (DKK () 1)

=> s l13 and l11
L14          2 L13 AND L11

=> d ibib 1-2

L14  ANSWER 1 OF 2     MEDLINE on STN
ACCESSION NUMBER:   2005314981     IN-PROCESS
DOCUMENT NUMBER:    PubMed ID: 15965110
TITLE:              How wnt signaling affects bone repair
                    by mesenchymal stem cells from the bone marrow.
AUTHOR:             Gregory Carl A; Gunn William G; Reyes Emigdio; Smolarz
                    Angela J; Munoz James; Spees Jeffrey L; Prockop Darwin J
CORPORATE SOURCE:   Center for Gene Therapy, Tulane University Health Sciences
                    Center, 1430 Tulane Avenue, New Orleans, LA 70112..
                    ca_gregory@hotmail.com
SOURCE:             Annals of the New York Academy of Sciences, (2005 May) 1049
                    97-106.
                    Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED;
                    Priority Journals
ENTRY DATE:         Entered STN: 20050621
                    Last Updated on STN: 20050621
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L14  ANSWER 2 OF 2     MEDLINE on STN
ACCESSION NUMBER:   2003612654     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 14695408
TITLE:              The role of the Wnt-signaling antagonist DKK1 in
                    the development of osteolytic lesions in
                    multiple myeloma.
COMMENT:            Comment in: N Engl J Med. 2003 Dec 25;349(26):2479-80.
                    PubMed ID: 14695406
                    Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                    reply 1464-6. PubMed ID: 15070800
                    Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                    reply 1464-6. PubMed ID: 15074002
                    Comment in: N Engl J Med. 2004 Apr 1;350(14):1464-6; author
                    reply 1464-6. PubMed ID: 15074001
                    Comment in: N Engl J Med. 2004 Jul 8;351(2):197-8. PubMed
                    ID: 15247367
AUTHOR:             Tian Erming; Zhan Fenghuang; Walker Ronald; Rasmussen Erik;
                    Ma Yupo; Barlogie Bart; Shaughnessy John D Jr
CORPORATE SOURCE:   Donna D. and Donald M. Lambert Laboratory of Myeloma
                    Genetics, Myeloma Institute for Research and Therapy,
                    College of Medicine, University of Arkansas for Medical
                    Sciences, Little Rock 72205, USA.
CONTRACT NUMBER:    CA55819 (NCI)
     CA97513 (NCI)
SOURCE:             New England journal of medicine, (2003 Dec 25) 349 (26)
                    2483-94.
                    Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200401
ENTRY DATE:         Entered STN: 20031230
                    Last Updated on STN: 20040107
                    Entered Medline: 20040106


=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1          3942 S WNT
L2           244 S L1 (S) ANTAGON?
L3        553450 S OSTEO? OR BONE
L4            70 S L3 AND L2
L5         22597 S MULTIPLE MYELOMA
L6             1 S L5 AND L4
L7             1 S L2 AND L5
L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
L11            7 S L10 AND L5
L12            1 S L11 NOT PY>2002
L13           70 S (DICKKOPF () 1) OR (DKK () 1)
L14            2 S L13 AND L11

=> d ibib kwic l12

L12  ANSWER 1 OF 1     MEDLINE on STN
ACCESSION NUMBER:   2001420323     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11468178
TITLE:              Identifying intercellular signaling genes expressed in
                    malignant plasma cells by using complementary DNA arrays.
```

AUTHOR: De Vos J; Couderc G; Tarte K; Jourdan M; Requirand G; Delteil M C; Rossi J F; Mechti N; Klein B
CORPORATE SOURCE: INSERM U475, Unit for Cellular Therapy, CHU Montpellier, 99 Rue Puech Villa, 34197 Montpellier Cedex 5, France.
SOURCE: Blood, (2001 Aug 1) 98 (3) 771-80.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20010917
Entered Medline: 20010913

AB In multiple myeloma (MM), the growth of primary plasma cells depends not only on interleukin-6 (IL-6), but also on additional unidentified signals delivered by the bone marrow environment. Using Atlas complementary DNA (cDNA) arrays comprising 268 genes coding for intercellular signaling molecules, this study identified genes. . . receptor (TR) that is linked to HB-EGF and syndecan-1 processing and to cell invasion, chemokine receptors CCR1 and CCR2, the Wnt pathway actor Frizzled-related protein (FRZB), and the Notch receptor ligand Jagged 2. These data, obtained with the Atlas cDNA array,. . .

CT B-Lymphocytes: ME, metabolism
Cell Division: DE, drug effects
Epidermal Growth Factor: ME, metabolism
Flow Cytometry
Gene Expression: GE, genetics
Humans
Multiple Myeloma: GE, genetics
*Multiple Myeloma: ME, metabolism
Multiple Myeloma: PA, pathology
Neoplasm Proteins: GE, genetics
Neoplasm Proteins: ME, metabolism
*Oligonucleotide Array Sequence Analysis: MT, methods
*Plasma Cells:. . .

```
=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1          3942 S WNT
L2           244 S L1 (S) ANTAGON?
L3        553450 S OSTEO? OR BONE
L4            70 S L3 AND L2
L5         22597 S MULTIPLE MYELOMA
L6             1 S L5 AND L4
L7             1 S L2 AND L5
L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
L11            7 S L10 AND L5
L12            1 S L11 NOT PY>2002
L13           70 S (DICKKOPF () 1) OR (DKK () 1)
L14            2 S L13 AND L11

=> s l13 and l3
L15           19 L13 AND L3

=> s l15 and express?
         932565 EXPRESS?
L16           14 L15 AND EXPRESS?
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=> s l16 not py>2002
       1489868 PY>2002
L17           6 L16 NOT PY>2002

=> d ibib 1-3

L17  ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002693855     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12455632
TITLE:              Bmp, Fgf and Wnt signalling in programmed cell death and
                    chondrogenesis during vertebrate limb development: the role
                    of Dickkopf-1.
AUTHOR:             Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE:   Institut fur Entwicklungs- und Molekularbiologie der Tiere
                    (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SOURCE:             International journal of developmental biology, (2002) 46
                    (7) 943-7.
                    Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY:       Spain
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200306
ENTRY DATE:         Entered STN: 20021214
                    Last Updated on STN: 20030619
                    Entered Medline: 20030618

L17  ANSWER 2 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002280313     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12021176
TITLE:              Global gene profiling in human endometrium during the
                    window of implantation.
AUTHOR:             Kao L C; Tulac S; Lobo S; Imani B; Yang J P; Germeyer A;
                    Osteen K; Taylor R N; Lessey B A; Giudice L C
CORPORATE SOURCE:   Department of Gynecology and Obstetrics, Stanford
                    University, Stanford, California 94305, USA.
CONTRACT NUMBER:    U54 HD31398 (NICHD)
SOURCE:             Endocrinology, (2002 Jun) 143 (6) 2119-38.
                    Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200206
ENTRY DATE:         Entered STN: 20020522
                    Last Updated on STN: 20020619
                    Entered Medline: 20020618

L17  ANSWER 3 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002131765     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11867524
TITLE:              The Wnt antagonist Dickkopf-1 is
                    regulated by Bmp signaling and c-Jun and modulates
                    programmed cell death.
AUTHOR:             Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE:   Entwicklungs- und Molekularbiologie der Tiere,
                    Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany..
                    lars.grotewold@uni-duesseldorf.de
SOURCE:             EMBO journal, (2002 Mar 1) 21 (5) 966-75.
                    Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200205
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ENTRY DATE: Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

=> d ibib 4-6

L17 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001447406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291860
TITLE: The role of the homeodomain protein Bozozok in zebrafish axis formation.
AUTHOR: Solnica-Krezel L; Driever W
CORPORATE SOURCE: Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SOURCE: International journal of developmental biology, (2001) 45 (1) 299-310.
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L17 ANSWER 5 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in Xenopus laevis.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: RO1 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

L17 ANSWER 6 OF 6 MEDLINE on STN
ACCESSION NUMBER: 1999425169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10495270
TITLE: Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AUTHOR: Monaghan A P; Kioschis P; Wu W; Zuniga A; Bock D; Poustka A; Delius H; Niehrs C
CORPORATE SOURCE: Division of Molecular Biology of the Cell I, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany.
SOURCE: Mechanisms of development, (1999 Sep) 87 (1-2) 45-56.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ243963; GENBANK-AJ243964
ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

=> d kwic 6

L17 ANSWER 6 OF 6 MEDLINE on STN
TI Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AB Dickkopf-1 (dkk-1) is member of a novel family of secreted proteins and functions in head induction during Xenopus embryogenesis, acting as a. . . of two additional murine members of the dkk family, dkk-2 and dkk-3; and (2) analysis of adult and embryonic gene expression of mouse dkk-1,-2, and -3, Xenopus dkk-1 as well as chicken dkk-3. Comparative developmental analyses of the dkk-1, dkk-2 and dkk-3 in mice indicate that these genes are both temporally and spatially regulated. They define overlapping deep domains in mesenchymal lineages suggesting a co-ordinated mode of action. All dkks show distinct and elevated expression patterns in tissues that mediate epithelial- mesenchyme transformations suggesting that they may participate in heart, tooth, hair and whisker follicle, limb and bone induction. In the limb buds expression of these genes are found in regions of programmed cell death. In a given organ, dkk-1 tends to be the earliest member expressed . Comparison with Xenopus dkk-1 and chicken dkk-3 shows evolutionarily conserved expression patterns. Our observations indicate that dkk genes constitute a new family of secreted proteins that may mediate inductive interactions between. . .
CT Amino Acid Sequence
Animals
Ectoderm: ME, metabolism
Epithelial Cells: ME, metabolism
*Gene Expression Regulation, Developmental
In Situ Hybridization
*Mesoderm: ME, metabolism
Mice
Molecular Sequence Data
*Proteins: GE, genetics
*Proteins: ME, metabolism
Reverse. . .

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.44	5.65

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 25 Jul 2005  VOL 143 ISS 5
FILE LAST UPDATED: 24 Jul 2005  (20050724/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s WNT
          4331 WNT
           330 WNTS
L18       4365 WNT
                (WNT OR WNTS)

=> s l1 (S) antagon?
          4331 WNT
           330 WNTS
          4365 WNT
                (WNT OR WNTS)
        270850 ANTAGON?
L19        273 L1 (S) ANTAGON?

=> s l18 (S) antagon?
        270850 ANTAGON?
L20        273 L18 (S) ANTAGON?

=> s myeloma
         16718 MYELOMA
           557 MYELOMAS
L21      16913 MYELOMA
                (MYELOMA OR MYELOMAS)

=> s l20 and l21
L22           5 L20 AND L21

=> d ibib 1-3

L22  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:450819  CAPLUS
DOCUMENT NUMBER:          142:461611
TITLE:                    Diagnosis, prognosis and identification of potential
                          therapeutic targets of multiple myeloma
                          based on gene expression profiling
INVENTOR(S):              Shaughnessy, John D.; Barlogie, Bart; Zhan, Fenghuang
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 80 pp., Cont.-in-part of U.S.
                          Ser. No. 454,263.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   4
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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     US 2005112630         A1    20050526    US 2004-931780           20040901
     US 2003175753         A1    20030918    US 2002-289746           20021107
     US 2003232364         A1    20031218    US 2003-409004           20030408
     US 2004009523         A1    20040115    US 2003-454263           20030604
PRIORITY APPLN. INFO.:                       US 2001-348238P     P    20011107
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L22 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:992468 CAPLUS
DOCUMENT NUMBER: 142:371352
TITLE: Wnt signaling antagonist DKK1 in the development of osteolytic lesion in multiple myeloma
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Institute of Clinical Endocrinology, Tokyo Women≈s Medical University, Tokyo, 162-8666, Japan
SOURCE: Ketsueki, Shuyoka (2004), 49(2), 166-170
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

L22 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:515641 CAPLUS
DOCUMENT NUMBER: 141:52350
TITLE: Expression of genes DKK1 and FRZB as molecular determinants of myeloma bone disease and transcription regulation for treatment thereof
INVENTOR(S): Shaughnessy, John D.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas, USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004053063	A2	20040624	WO 2003-US38372	20031204
WO 2004053063	A3	20041125		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004137489	A1	20040715	US 2003-727461	20031204
PRIORITY APPLN. INFO.:			US 2002-431040P P	20021205

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L22 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:40999 CAPLUS
DOCUMENT NUMBER: 140:109553
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Zhan, Fenghuang; Barlogie, Bart
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 67 pp., Cont.-in-part of U.S. Ser. No. 409,004.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004009523	A1	20040115	US 2003-454263		20030604
US 2003175753	A1	20030918	US 2002-289746		20021107
US 2003232364	A1	20031218	US 2003-409004		20030408
US 2005112630	A1	20050526	US 2004-931780		20040901
PRIORITY APPLN. INFO.:			US 2001-348238P	P	20011107
			US 2002-355386P	P	20020208
			US 2002-403075P	P	20020813
			US 2002-289746	A2	20021107
			US 2003-409004	A2	20030408
			US 2003-454263	A2	20030604

L22 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:1011522 CAPLUS
DOCUMENT NUMBER: 140:126264
TITLE: The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma
AUTHOR(S): Tian, Erming; Zhan, Fenghuang; Walker, Ronald; Rasmussen, Erik; Ma, Yupo; Barlogie, Bart; Shaughnessy, John D., Jr.
CORPORATE SOURCE: Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics, Myeloma Institute for Research and Therapy, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
SOURCE: New England Journal of Medicine (2003), 349(26), 2483-2494
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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             8 DICKKOPFS
           177 DICKKOPF
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           104 DICKKOPF (W) 1
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            11 DKKS
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                 (DICKKOPF OR DICKKOPFS)
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                 (DICKKOPF(W)1)
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L25         170 L23 OR L24

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L26       61795 OSTEO?

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L27          32 L26 AND L25

=> d his

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     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
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L3        553450 S OSTEO? OR BONE
L4            70 S L3 AND L2
L5         22597 S MULTIPLE MYELOMA
L6             1 S L5 AND L4
L7             1 S L2 AND L5
L8         31029 S MYELOMA
L9             1 S L8 AND L2
L10          451 S L1 AND L3
L11            7 S L10 AND L5
L12            1 S L11 NOT PY>2002
L13           70 S (DICKKOPF () 1) OR (DKK () 1)
L14            2 S L13 AND L11
L15           19 S L13 AND L3
L16           14 S L15 AND EXPRESS?
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     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
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L19          273 S L1 (S) ANTAGON?
L20          273 S L18 (S) ANTAGON?
L21        16913 S MYELOMA
L22            5 S L20 AND L21
L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25

=> s l27 and l21
L28            7 L27 AND L21

=> d ibib 1-4

L28  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:450819  CAPLUS
DOCUMENT NUMBER:          142:461611
TITLE:                    Diagnosis, prognosis and identification of potential
                          therapeutic targets of multiple myeloma
                          based on gene expression profiling
INVENTOR(S):              Shaughnessy, John D.; Barlogie, Bart; Zhan, Fenghuang
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 80 pp., Cont.-in-part of U.S.
                          Ser. No. 454,263.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   4
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005112630	A1	20050526	US 2004-931780		20040901
US 2003175753	A1	20030918	US 2002-289746		20021107
US 2003232364	A1	20031218	US 2003-409004		20030408
US 2004009523	A1	20040115	US 2003-454263		20030604
PRIORITY APPLN. INFO.:			US 2001-348238P	P	20011107
			US 2002-355386P	P	20020208
			US 2002-403075P	P	20020813
			US 2002-289746	A2	20021107
			US 2003-409004	A2	20030408
			US 2003-454263	A2	20030604

L28 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:348815 CAPLUS
DOCUMENT NUMBER: 142:397651
TITLE: Inhibitors of protein Dickkopf-1 for treating osteolytic lesions in multiple myeloma and enhancing osteogenesis
INVENTOR(S): Prockop, Darwin; Gregory, Carl; Gunn, William
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 84 pp., Cont.-in-part of U.S. Ser. No. 830,352, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005084494	A1	20050421	US 2004-839515		20040505
US 2004235166	A1	20041125	US 2003-442506		20030521
PRIORITY APPLN. INFO.:			US 2003-442506	A2	20030521
			US 2004-830352	B2	20040422

L28 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:992468 CAPLUS
DOCUMENT NUMBER: 142:371352
TITLE: Wnt signaling antagonist DKK1 in the development of osteolytic lesion in multiple myeloma
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Institute of Clinical Endocrinology, Tokyo Women≈s Medical University, Tokyo, 162-8666, Japan
SOURCE: Ketsueki, Shuyoka (2004), 49(2), 166-170
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

L28 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:515641 CAPLUS
DOCUMENT NUMBER: 141:52350
TITLE: Expression of genes DKK1 and FRZB as molecular determinants of myeloma bone disease and transcription regulation for treatment thereof
INVENTOR(S): Shaughnessy, John D.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas, USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004053063	A2	20040624	WO 2003-US38372		20031204
WO 2004053063	A3	20041125			
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004137489	A1	20040715	US 2003-727461		20031204
PRIORITY APPLN. INFO.:			US 2002-431040P	P	20021205

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L28 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:504577 CAPLUS
DOCUMENT NUMBER: 141:219048
TITLE: Activation mechanism of osteoclasts
AUTHOR(S): Sato, Kanji
CORPORATE SOURCE: Dep. of Medicine II, Tokyo Women's Medical University, Tokyo, 162-8666, Japan
SOURCE: Ketsueki, Shuyoka (2004), 48(3), 274-280
CODEN: KETSBI; ISSN: 0915-8529
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

L28 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:40999 CAPLUS
DOCUMENT NUMBER: 140:109553
TITLE: Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling
INVENTOR(S): Shaughnessy, John D.; Zhan, Fenghuang; Barlogie, Bart
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 67 pp., Cont.-in-part of U.S. Ser. No. 409,004.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004009523	A1	20040115	US 2003-454263		20030604
US 2003175753	A1	20030918	US 2002-289746		20021107
US 2003232364	A1	20031218	US 2003-409004		20030408
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PRIORITY APPLN. INFO.:			US 2001-348238P	P	20011107
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			US 2003-454263	A2	20030604

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L28  ANSWER 7 OF 7  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:1011522  CAPLUS
DOCUMENT NUMBER:          140:126264
TITLE:                    The role of the Wnt-signaling antagonist DKK1
                          in the development of osteolytic lesions in
                          multiple myeloma
AUTHOR(S):                Tian, Erming; Zhan, Fenghuang; Walker, Ronald;
                          Rasmussen, Erik; Ma, Yupo; Barlogie, Bart;
                          Shaughnessy, John D., Jr.
CORPORATE SOURCE:         Donna D. and Donald M. Lambert Laboratory of Myeloma
                          Genetics, Myeloma Institute for Research and Therapy,
                          College of Medicine, University of Arkansas for
                          Medical Sciences, Little Rock, AR, USA
SOURCE:                   New England Journal of Medicine (2003), 349(26),
                          2483-2494
                          CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER:                Massachusetts Medical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          41    THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                    40.47      46.12

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FILE LAST UPDATED:          19 JUL 2005      <20050719/UP>
MOST RECENT UPDATE WEEK:       200528         <200528/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

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            181 DKK
                  (DKK OR DKKS)
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=> s l32 or l31
L33          62 L32 OR L31

=> s osteo?
L34       27031 OSTEO?

=> s l34 or bone
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           8795 BONES
          50481 BONE
                  (BONE OR BONES)
L35       59451 L34 OR BONE

=> s cancer? or tumor? or neoplas?
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          58772 TUMOR?
          20120 NEOPLAS?
L36       87552 CANCER? OR TUMOR? OR NEOPLAS?

=> s myeloma
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L37       14570 MYELOMA
                  (MYELOMA OR MYELOMAS)

=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1         3942 S WNT
L2          244 S L1 (S) ANTAGON?
L3       553450 S OSTEO? OR BONE
L4           70 S L3 AND L2
L5        22597 S MULTIPLE MYELOMA
L6            1 S L5 AND L4
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L15          19 S L13 AND L3
L16          14 S L15 AND EXPRESS?
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     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18        4365 S WNT
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L20          273 S L18 (S) ANTAGON?
L21        16913 S MYELOMA
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L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25
L28            7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
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L34        27031 S OSTEO?
L35        59451 S L34 OR BONE
L36        87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37        14570 S MYELOMA

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L62 NOT FOUND
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of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

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L39          18 L38 AND L37

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L42           1 L41 AND L40

=> d ibib

L42    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2002066509 PCTFULL  ED 20020910  EW 200235
TITLE (ENGLISH):         TREATMENT INVOLVING DKK-1 OR
                         ANTAGONISTS THEREOF
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TITLE (FRENCH): TRAITEMENT FAISANT APPEL A DKK-1 OU AUX ANTAGONISTES DE DKK-1

INVENTOR(S): DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116, San Mateo, CA 94403, US;
STEWART, Timothy A., 465 Douglas Street, San Francisco, CA 94114, US

PATENT ASSIGNEE(S): GENENTECH, INC., 1 DNA Way, South San Francisco, CA 94080, US [US, US]

AGENT: HASAK, Janet E.$, GENENTECH, INC., MS 49, 1 DNA Way, South San Francisco, CA 94080-4990$, US

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002066509	A2	20020829

DESIGNATED STATES

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RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-US4573 A 20020215

PRIORITY INFO.: US 2001-60/269,435 20010216

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(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

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L3 553450 S OSTEO? OR BONE
L4 70 S L3 AND L2
L5 22597 S MULTIPLE MYELOMA
L6 1 S L5 AND L4
L7 1 S L2 AND L5
L8 31029 S MYELOMA
L9 1 S L8 AND L2
L10 451 S L1 AND L3
L11 7 S L10 AND L5
L12 1 S L11 NOT PY>2002
L13 70 S (DICKKOPF () 1) OR (DKK () 1)
L14 2 S L13 AND L11
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L16 14 S L15 AND EXPRESS?
L17 6 S L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005

L18 4365 S WNT
L19 273 S L1 (S) ANTAGON?
L20 273 S L18 (S) ANTAGON?
L21 16913 S MYELOMA
L22 5 S L20 AND L21
L23 123 S (DICKKOPF () 1) OR (DKK () 1)
L24 155 S DICKKOPF-1 OR DKK1
L25 170 S L23 OR L24
L26 61795 S OSTEO?

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L27           32 S L26 AND L25
L28            7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29         1307 S WNT
L30          161 S L29 (S) ANTAG?
L31           46 S (DICKKOPF () 1) OR (DKK () 1)
L32           62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33           62 S L32 OR L31
L34        27031 S OSTEO?
L35        59451 S L34 OR BONE
L36        87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37        14570 S MYELOMA
L38           39 S L33 AND L34
L39           18 S L38 AND L37
L40            8 S L39 NOT PY>2002
L41           10 S L33/CLM
L42            1 S L41 AND L40

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        221598 1/AB
             3 DICKKOPF-1/AB
                 ((DICKKOPF(W)1)/AB)
             1 DKK1/AB
             5 DKK/AB
        221598 1/AB
             2 DKK-1/AB
                 ((DKK(W)1)/AB)
             5 DICKKOPF/AB
        221598 1/AB
             3 DICKKOPF/AB (W) 1/AB
             5 DKK/AB
        221598 1/AB
             2 DKK/AB (W) 1/AB
L43          4 ((DICKKOPF-1/AB OR DKK1/AB OR DKK-1/AB) OR ((DICKKOPF/AB (W)
               1/AB) OR (DKK/AB (W) 1/AB)))

=> s l42 and l35
L44          1 L42 AND L35

=> d ibib

L44    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2002066509 PCTFULL  ED 20020910  EW 200235
TITLE (ENGLISH):         TREATMENT INVOLVING DKK-1 OR
                         ANTAGONISTS THEREOF
TITLE (FRENCH):          TRAITEMENT FAISANT APPEL A DKK-1 OU
                         AUX ANTAGONISTES DE DKK-1
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=> d kwic

L44    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2005 Univentio on STN
TIEN   TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
TIFR   TRAITEMENT FAISANT APPEL A DKK-1 OU AUX ANTAGONISTES
       DE DKK-1
ABEN   Antagonists to Dickkopf-1 (Dkk-1
       ) proteins are administered in effective amounts to treat disorders
       involving insulin resistance, such as non-insulin-dependent diabetes
       mellitus (NIDDM), hypoinsulinemia, and disorders involving muscle
       atrophy, trauma, or degeneration. Preferably, the antagonists are
       composed of compositions comprising antibodies directed to Dkk
       -1 in a pharmaceutically acceptable carrier for use in
       blocking the effects of Dkk-1. Additionally provided
       is a method of treating obesity or hyperinsulinemia in a mammal by
       administering an effective amount of Dkk-1 to a
       mammal. Also provided are methods of diagnosing insulin resistance,
       hyper- and hypoinsulinemia, obesity, and related disorders using
       Dkk-1 as a target and non-human transgenic animals
       that overexpress <i>dkk-1</i> nucleic acid.
ABFR   L'invention concerne un traitement consistant a administrer des
       antagonistes des proteines Dickkopf-1 (Dkk
       -1) en quantites efficaces pour traiter les troubles
       impliquant une resistance insulinique, tels que le diabete non
       insulino-dependant (NIDDM), l'hypoinsulinemie et les troubles impliquant
       une atrophie musculaire, un traumatisme ou une degeneration. Ces
       antagonistes sont avantageusement composes d'anticorps diriges contre
       Dkk-1 dans un excipient pharmaceutiquement acceptable
       et utilises pour bloquer les effets de Dkk-1.
       L'invention concerne egalement une methode de traitement de l'obesite ou
       de l'hyperinsulinemie chez un mammifere, consistant a administrer une
       quantite efficace de Dkk-1 a un patient. L'invention
       concerne egalement des methodes permettant de diagnostiquer la
       resistance insulinique, l'hyper- et l'hypoinsulinemie, l'obesite et les
       troubles associes, a l'aide de Dkk-1 comme cible et
       des animaux transgeniques non humains surexprimant l'acide nucleique <i>
       dkk-1</i>.

DETD   TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
       Background of the Invention
       Field of the Invention
       The present invention provides for the diagnosis and treatment of
       disorders involving. . . hyperinsulinemia and for repairing and
       regenerating muscle in
       mammals. More particularly, the present invention relates to the use of
       Dickkopf- I (Dkk- 1) protein to treat
       obesity and hyperinsulinemia and to the use of antagonists that bind to
       Dkk- I and/or neutralize its activity. . .

       Dkk-I (WO 99/46281 published Sept. 16, 1999, wherein the Dkk-
       1 is designated as PRO1008 and is
```

encoded by DNA57530; WO 00/18914 published April 6, 2000; WO 00/52047 published September 8,
2000; WO. . .
. . .
as polycystic ovarian disease, dermatological
disorders such as infections, varicose veins, Acanthosis nigricans, and eczema, exercise intolerance, insulin
resistance, hypertension, hypercholesterolernia, cholelithiasis, osteoarthritis, orthopedic injury,
thromboembolic disease, cancer, and coronary heart disease. Rissanen et al., British Medical Journal, 301.

t]
Summary of the Invention
Accordingly, antagonists to Dkk-1, such as
antibodies, are herein disclosed to be useful in the
treatment of insulin resistance associated with, for example, glucose intolerance,. . .
. . .
mammal in need thereof an
effective amount of an antagonist to Dkk Preferably, the mammal is human, the Dkk-I is human Dkk-1,
and/or the human has NIDDM. Also preferred is systemic administration. The antagonist is preferably,an
antibody that binds Dkk- 1, and more preferably a
monoclonal antibody that binds Dkk- 1, and still
more
preferably one that neutralizes an insulin-resistance or hypoinsulinernic activity of Dkk Most preferred is
a monoclonal antibody prepared from. . .

Preferably, the measuring is carried out using an anti-Dkk-
1 antibody, such as a monoclonal
antibody, in an immunoassay, Also, preferably such anti-Dkk-
1 antibody comprises a label, more preferably
a fluorescent label, a radioactive label, or an enzyme label, such as a bioluminescent label. . .

5
Additionally provided is a monoclonal antibody preparation prepared by hyperimmunizing mice
with tagged Dkk- 1 (preferably purified recombinant
polyhistidine-tagged human Dkk-I) diluted in an
adjuvant, fusing B-cells from the mice having anti-Dkk-
1 antibody titers (preferably high titers) with mouse
myelorna cells and obtaining supernatants, harvesting the supernatants, screening the harvested supernatants
for antibody production,. . .
. . .
a candidate pharmaceutical drucr
on insulin resistance, hypoinsulinernia, or muscle repair comprising administering said drug to a non-human
transgenic animal that overexpresses dkk-1 nucleic
acid and determining the effect of the drug on glucose
clearance from the blood of said animal, on circulating insulin. . .
the animal is a rodent, more preferably a mouse or rat, and most preferably a mouse. In another preferred embodiment, the dkk-
1 nucleic acid overexpressed by the animal is
under the control of a muscle-specific promoter, and the cDNA is overexpressed in muscle. . .

(a) a container comprising an antibody that binds Dkk-1;
(b) a container comprising a standard sample containing Dkk-
1; and
(c) instructions for using the antibody and standard sample to detect

insulin resistance, hypoinsulinemia,
hyperinsulinemia, or obesity, wherein either the antibody. . . is
detectably labeled or the kit
further comprises another container comprising a second antibody that is
detectably labeled and binds to the
Dkk-1 or to the antibody that binds Dkk Preferably
the anti-Dkk-1 antibody of the kit is a monoclonal
antibody, more preferably one that neutralizes an insulin-resistance,
hyperinsulinemic, hypoinsulinemic, or
obesity activity of Dkk-1.

. . .
for detecting the presence or onset of obesity or
hyperinsulinemia in a mammal comprising the steps of-
(a) measuring the amount of Dkk-1 in a sample from
said mammal; and
(b) comparing the amount determined in step (a) to an amount of Dkk-1
present in a standard sample, a
decreased level in the amount of Dkk-1 in step (a)
being indicative of obesity or hyperinsulinemia.

Preferably, the measuring is carried out using an anti-Dkk-
1 antibody in an immunoassay. Also,
preferably the anti-Dkk- I antibody comprises a label. The preferred
labels and immunoassays are those as
6
set. . .

In a preferred embodiment the Dkk- I is human Dkk- 1
in the kit and it may further comprise a container with
a weight-loss agent.

. . .
effect of a candidate pharmaceutical drug
on obesity or hyperinsulinernia comprising administering said druo, to a
non-human binary transgenic animal
that expresses dkk-1 nucleic acid and determining
the effect of the drug on an obesity-determining property or
on the level of insulin in said. . .

The invention also provides a non-human transgenic animal that
overexpresses dkk-1 nucleic acid.

. . .
method for repairing or regenerating muscle in a mammal comprising
administering to the mammal an effective amount of an antagonist to
Dkk-1, preferably an antibody that
binds to Dkk Preferably, the mammal is human and/or the antibody is a
monoclonal antibody.

(a) a container comprising an antagonist toDkk- 1, preferably an
antibody that binds Dkk- 1; and
(b) instructions for using the antagonist to repair or regenerate muscle
in a mammal.

Figure 2 shows a gel of human Dkk-1 expressed in
baculovirus and its clipping.

Figure 3A shows the effects of human Dkk- 1 (dark
bars) on basal glucose uptake in L6 muscle cells
for 2, 6, and 26 hours. Figures 3B and 3C show, respectively, the
effects of human Dkk-1 on basal (light
bars) and 30 nM-insulin-stimulated (dark bars) glucose uptake in L6
muscle cells.

. . .
shows the effects of human Dkk]l on basal and
insulin-dependent glucose uptake (expressed as percent control) as a
function of human Dkk-1 concentration

(nM) upon 48-hour treatment.

Figure 5A-513 show respectively the effect of human Dkk-1 on the incorporation of glucose into glycogen in L6 muscle cells with (dark bars) and without (light bars) insulin for 48. . .

Ficrures 8A-8D show the effect of 40 nM human Dkk-1 (dark bars) on the kinase activities of PDK-I (Fig. 8A), GSK3 P (Fig. 813), S6 kinase (Fig. SC), and Akt (Fig.. . .

Figures 9A and 9B show the effect of human Dkk-1 on levels of basal (light bars) and 30 nM-insulin-stimulated (dark bars) criucose uptake of 3T3 LI cells (adipocytes) after 48-hour. . .

. . .
Dkk-I (triangles). Figure I IB shows the insulin levels in the female FVB mice intravenously injected with saline (control), 0.05 mg/kg/day human Dkk-1, and 0.2 mg/kg/day human Dkk Figure 12A shows the effects of human Dkk-1 on expression of various markers of muscle differentiation in mice injected therewith, with control (light bars) and 0.2 mg/kg/day of human. . .

Figure 17 shows the effect of an anti-human Dkk-1 monoclonal antibody on the Dkk-1-mediated decrease in glucose uptake in L6 cells in the absence and presence of insulin, where the. . . the L6 cells with 40 nM Dkk-I are black bars, and the L6 cells with 40 nM Dkk-I and 0.5 [tg/mL anti-Dkk-1 antibody are dark gray bars on the far right.

An insulin-resistance-treating agent is an agent other than an antagonist to Dkk-1 that is used to treat insulin resistance, such as, for example, hypoglycemic agents. Examples of such treating agents include insulin (one or. . .

As used herein, Dkk- I or Dickkopf- 1 refers to Wnt inhibitor with properties and characteristics described in WO 99/46281 published September 16, 1999 and Glinka et aL, Nature,. . .

The expressions, antagonist, antagonist to Dkk-1, and the like within the scope of the present invention are meant to include any molecule that interacts with Dkk-1 and interferes with its function or blocks or neutralizes a relevant activity of Dkk- 1, by whatever means, depending on the indication being treated. It may prevent the interaction between Dkk-1 and one or more of its receptors. Such agents accomplish this effect in various ways. For instance, the class of antagonists that neutralize a Dkk-1 activity will bind to Dkk- I with sufficient affinity and specificity to interefere with Dkk- I as defined below.

An antibody that binds Dkk- 1 is one capable of bindin cr that antigen with sufficient affinity such that the antibody is useful as a therapeutic agent. . . the Dkk Included within this group of antagonists are, for example, antibodies directed against Dkk- I or portions thereof reactive with Dkk-1, the Dkk- I receptor or portions thereof reactive with Dkk-I, or any other licrand that binds to Dkk The term also. . .

. . .
neutralize the activity of are used herein to mean, for example, block, prevent, reduce, counteract the activity of, or make the Dkk-1 ineffective by any mechanism. Therefore, the antagonist may prevent a binding event necessary for activation of Dkk By neutralizing antibody is meant an antibody molecule as herein defined that is able to block or significantly reduce an effector function of the Dkk- 1. For example, a neutralizing antibody may inhibit or reduce the ability of Dkk- I to interact with a Dkk- I receptor. Alternatively, the neutralizing antibody may inhibit or reduce the ability of Dkk- 1 to block the Dkk- I receptor signalling pathway. The neutralizing antibody may also immunospecifically bind to the Dkk-1 in an immunoassay for Dkk-I activity such as the ones described herein. It is a characteristic of the neutralizing antibody of. . .

The term non-human transgenic animal that overexpresses dkk-1 nucleic acid herein refers to a non-human animal, such as a rodent, that has included within a plurality of its cells. . .

The term non-human binary transgenic animal that expresses dkk-1 nucleic acid herein refers to a non-human animal, such as a rodent, in which gene expression is controlled by the interaction of Dkk-1 on a
16
target transgene. These interactions are controlled by crossing animal lines (such as rodent, e.g., mouse lines) or by adding or. . .

. . .
diagnosing and treating insulin resistance and hypoinsulinemia based on antagonists that bind to, and preferably neutralize, the activity of Dkk
Further, Dkk- 1 itself is a useful treatment for obesity and hyperinsulinemia.

Additionally, antagonists to Dkk-1 are further indicated in methods herein for muscle repair and regeneration.

. . .
will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp. . .

. . .
in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin,. . .

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to. . . .

Among these, preferred myeloma cell lines are murine

myeloma lines, such as those derived from MOPC-21 and MPC- I I mouse tumors available from the Salk Institute Cell Distribution Center,. . .

. . .

which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles. . .

Amino acid sequence modification(s) of the anti-Dkk-1 antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the. . . Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the anti-Dkk-1 antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses. . .

. . .

or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an anti-Dkk-1 antibody with an N-terminal methionyl residue or the antibody fused to a hypoglycemic polypeptide. Other insertional variants of the anti-Dkk- I antibody. . .

. . .

preparation by oligonucleotide-mediated (or site-directed) mutacrenesis, PCR niutagenesis, or cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-Dkk- 1 antibody.

. . .

serum half-life of the therapeutic antagonist. For example, a soluble immunoglobulin chimera, such as described herein, can be obtained for each specific Dkk-1 antagonist or antagonistic portion thereof, as described in U.S. Pat. No.

. . .

The preferred dose is about 0 50 mg/kg/day, more preferably about 0. I to 25 mg/kg/day. More preferred still, when the Dkk- 1 antagonist is administered daily, the intravenous or intramuscular dose for a human is about 0.3 to 10 mg/kg of body weight. . .

. . .

Preferred continuous dosing schedules include daily continuous infusion, where Dkk- I antagonist is infused each day, and continuous bolus administration schedules, where Dkk-1 antagonist is administered at least once per day by bolus injection or inhalant or intranasal routes. The invention also encompasses discontinuous. . .

. . .

will vary according to the formulation, method of delivery, and clinical needs of the mammal being treated. For example, if the Dkk- 1 antagonist is administered by infusion, administration schedules may comprise a first period of administration followed by a second period in which Dkk-. . .

. . .

the administration is by bolus injection, especially bolus injection of a slow-release

formulation, dosing schedules may also be continuous in that Dkk -1 antagonist is administered each day, or may be discontinuous, with first and second periods as described above. . . .

dosing schedule, and route of administration for the treatment of the insulin-resistant or hypoinsulinemic disorder or muscle condition. The containers of Dkk-1 antagonist may be unit doses, bulk packages (e.g., multi-dose packages), or sub-unit doses. . . .

resilient stopper. Ampoules with non-resilient, removable closures (e.g., sealed glass) or resilient stoppers are most conveniently used for injectable forms of Dkk-1 antagonist. Also contemplated are packages for use in combination with a specific device, such as an inhaler, a nasal administration device. . . .

One specifically preferred method for administration of Dkk-1 is by subcutaneous infusion, particularly using a metered infusion device, such as a pump. Such pump can be reusable or disposable,. . .

Therapeutic formulations of Dkk-1 suitable for storage include mixtures of the Dkk-1 having the desired degree of purity with pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)),. . . are described in WO 97/04801. These compositions comprise Dkk- I containing from about 0.1 to 90% by weight of the active Dkk-1, preferably in a soluble form, and more generally from about 10 to 30%. . . .

methods. In addition, sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the Dkk-1, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example,. . .

The Dkk-1 can bejoined to a carrier protein or PEG or POG or other molecule of this nature to increase its serum half-life,. . .

For treatment of hyperinsulinemia, the administration of Dkk-1 may occur in conjunction with, for example, diazoxide (see, for example, Shaer, Nephron, 89: 337-339 (2001)).

For treatment of obesity, the administration of Dkk-1 may occur without, or may be imposed with, a dietary restriction such as a limit in daily food or calorie intake, as is desired for the individual patient. In addition, the Dkk-1 is appropriately administered in combination with other treatments for combatting or preventing obesity, known herein as weight-loss agents. Substances useful for. . . .

These weight-loss adjunctive agents and diazoxide may be administered at the same time as, before, or after the administration of the Dkk-1 and can be administered by the same or a different administration route than the Dkk- I is administered.

The dosages of Dkk-1 administered to an obese or hyperinsulinemic mammal will be determined by the physician in the light of the relevant circumstances, including the condition of the mammal, the type of Dkk-1, and the chosen route of administration. The dosage is preferably at a sufficiently low level as not to cause insulin-resistance, and. . . The preferred dose is about 0 50 32 mg/kg/day, more preferably about 0. I to 25 mg/kg/day. More preferred still, when the Dkk- 1 is administered daily, the intravenous or intramuscular dose for a human is about 0.3 to 10 mc,,r/kg of body weight per. . .

. . .

Dkk-I is administered by infusion, administration schedules may comprise a first period of administration followed by a second period in which Dkk-1 is not administered that is greater than, equal to, or less than the first period.

. . .

also provides kits for the treatment of obesity or hyperinsulinemia. The kits of the invention comprise one or more containers of Dkk- 1, preferably human Dkk- 1, in combination with a set of instructions, generally written instructions, relating to the use and dosage of Dkk- I for the. . .

Dkk- I may be packaged in any convenient, appropriate packaging. For example, if the Dkk- 1 is a freeze-dried formulation, an ampoule with a resilient stopper is normally used, so that the drug may be easily reconstituted by. . .

In one embodiment, one or more of the anti-Dkk-1 antibodies used in the assay is labeled; in another embodiment, a first is unlabeled, and a labeled, second antibody is used. . .

. . .

I antibody need not be labeled, and the presence thereof can be detected using a labeled antibody which binds to the Dkk-1 antibody.

In the assays of the present invention, an antigen such as Dkk -1, or an antibody is preferably bound to a solid phase support or carrier. By solid phase support or carrier is intended. . .

. . .

a solid phase matrix, preferably a microplate. The sample is brought in contact with the Ab I -coated matrix such that any Dkk-1 in the sample to which AM is specific binds to the solid-phase Abl. Unbound sample components are removed by washing. An. . .

. . .

the diagnostic assay. For instance, such a kit can comprise an antibody or antibodies, preferably a pair of antibodies to the Dkk- 1 anti cren that preferably do not compete for the same binding site on the antigen. In a specific embodiment, Dkk-1 may be pre-adsorbed to the solid phase matrix. The kit preferably contains the other necessary washing reagents well-known in the art.. . . the art, and some are exemplified below. The kit can optionally also comprise a Dkk-I standard; ie., an amount of purified Dkk- 1 corresponding to a normal amount of Dkk- I in a standard sample.

In one aspect, a kit comprises in more than one container: an antibody that binds Dkk-1, which can
be coated on a solid-phase carrier, e.g., a microtiter plate, a standard sample containing Dkk-1, and
instructions for use in detection, wherein the antibody that binds Dkk-I is detectably labeled or the kit further
comprises an. . .

. . .

cDNA such as inurine cDNA encoding Dkk- I or an appropriate sequence thereof can
be used to clone genomic DNA encoding Dkk-1 in
accordance with established techniques, and the genomic
sequences are used to generate trans crenic animals that contain cells that express DNA encoding Dkk- 1.

. . .

transgene incorporation with tissue-specific enhancers, which
results in targeted overexpression of Dkk Transgenic animals that include a copy of a transgene encoding
Dkk-1 introduced into the crerm line of the animal
at an embryonic stage can be used to examine the effect of
increased. . .

. . .

a probe that is complementary to at least a portion of the transgene.
Western blot analysis
using an antibody against the Dkk-1 encoded by the
transcrene may be employed as an alternative or
additional method for screenina for the presence of the transcrene. .

.

. . .

specific type of cell. The most preferred such control element herein is a muscle-
specific promoter that enables overexpression of the dkk-
1 nucleic acid (e.g., cDNA) in muscle tissue. An
example of such promoter is that described in Example I below or that.

. .

40

In another facet, non-human binary transgenic animals having altered dkk-1 nucleic acid expression
can be used to screen candidate drugs as set forth above, such as for their ability to reduce. . .

Example 1
Effects of Dkk-1 itz vivo and in vitro
Materials and Methods
L6 Cell culture
L6 myoblasts were proliferated in growth medium, composed of MEM alpha (Gibco-BRL). . . differentiation medium at
confluence (MEM alpha with 2% fetal calf serum). Cells were grown in this medium for 3-9 days and for
Dkk-1 treatments longer than 28 hours, dkk--1
(Krupnik et al., supra; WO 99/46281; DNA encoding
PRO1008) was added to this medium. Treatments. . .

Expression of Recombinant Dkk-I
The human homolog of Dkk-1 (hDkk-1) was expressed as
a C-terminal 8X His tag fusion (see
Krupnik et al., supra; and WO 99/46281, where PRO1008 is Dkk-1) in baculovirus and purified by nickel
affinity column chromatography. The identity of purified protein was verified by N-terminal sequence
analysis. The purified. . .

Glycogen Synthesi
Glycogen synthesis was determined as [14 Clglucose incorporation into

glycooren. Control L6 cells
and cells treated with dkk-1 were incubated for 2
hours in serum-free MEM alpha containing [U-14 Q glucose
(5 mM crlucose; 1.25 pCi/n-d) with or without. . .
. . .
Chem., 253: 7570-7578 (1978)). Differentiated cells were treated with
Dkk-I at 72 hours after the induction
of differentiation. For effect of Dkk-1 on 3T3L1
cell differentiation, Dkk-I was added to the medium at a
concentration of 40 nM during the initiation of differentiation. . .
. . .
3' to the pRK splice donor/acceptor site
that was preceded by the myosin light-chain promoter (Shani, Nature,
314: 283-286 (1985)). The dkk-1
cDNA was followed by the splice donor/acceptor sites present between the
fourth and fifth exons of the
human growth hormone gene (Stewart. . .

When expressed in baculovirus, the human Dkk-1
protein was clipped internally to give a 16-kDa
cleavage product. In the gel shown in Fig. 2, band (a) corresponds to.
. . .

The Dkk-1 effects of glucose uptake are independent
of the differentiation state of the cells and can
be seen even in cells that. . . uptake are dose-dependent. Fig. 4B
shows that the decrease in basal and insulin-dependent glucose
uptake is seen upon 48-hour treatment with Dkk-1 at
concentrations as low as 10 nM.
. . .
regulated the expression of genes in the insulin
signaling pathway in L6 muscle cells. In particular, as shown in Fig. 7,
Dkk-1 treatment increased the
expression of the p85 subunit of phosphoinositide 3-kinase significantly
(8.3 fold) following 48-hour
treatment, but did not significantly affect. . .
. . .
Dkk- I in mice resulted in impaired glucose tolerance and
reduced insulin production. Specifically, to confirm the in vivo effects
of Dkk-1 seen in transgenic mice,
female FVB mice were injected intravenously with Dkk-1 for 8 days
(single daily injection of 0.05 and 0.2
mg/kg/day). The effects of Dkk- 1 on glucose
tolerance were measured 48 hours and 8 days after the start of
injection. Glucose tolerance was unaffected with 48. . .

Overexpression of Dkk-1 in mice affected growth, body composition, and
metabolism. Particularly,
Transcrenic FVB mice overexpressing the dkk-1
transgene under control of the MLC promoter were
generated (Shani, supra). Body weights of control and transgenic animals
were followed over. . .

45
Table 2
Control Control Dkk-I Dkk-1
Regular diet Regular diet transgenic transgenic
Physiological Parameter (males, n=8) (females, n=4) Regular diet Regular
diet
males, n=4) (females, n=8)
Body Weight at 16. . .
. . .
signaling inhibits adipogenesis. To determine whether Dkk-I affected
body composition, some
animals were placed on a high-fat diet for 24 weeks. Dkk-

1 transgenic animals on a high-fat diet also showed significantly reduced body weights than their wild-type littermates (Fig. 15A), with comparable reduction. . .

46
Table 3
Control Control Dkk-1 TG Dkk-1 TG
High-fat diet High-fat diet High-fat diet High-fat diet
eter (m--12) (f=8) m=6) (f=5)
Body Weight at 16 of
40.3 ± 6.6 34.7 ±. . .
. . .
diabetes, can be affected by expression levels, phosphorylation, and activity of
proteins in the insulin- signaling pathway. Therefore, the effects of Dkk-1 in muscle both in vivo and in vitro
were investigated.
. . .
animals also had reduced levels of serum insulin, although no effects were seen in the serum insulin levels in transgenic mice. Dkk-1 reduced the basal and insulin-stimulated
glucose uptake in L6 cells through inhibition of Akt, a key intermediate in the insulin-signaling pathway.

These effects of Dkk-1 were seen only after 18 hrs of exposure to Dkk-1.
. . .
size with a proportional decrease in the
weight of various organs. Without beinor limited to any one theory, these effects of Dkk-1 are likely to be
mediated through the reduction in insulin (and likely IGF-1)-stimulated Akt activity. Direct evidence for this
comes from studies. . .

Chem., 276: 19664-19671 (2001)). Alternatively, without limitation to any one theory, the reduced growth
rate in dkk-1 transgenic animals could be a
secondary effect of the reduced glucose uptake and consequent alteration in nutrient availability and metabolic rate. . .

Primary 3T3LI preadipocytes were stimulated to differentiate in the presence or absence of Dkk-1,
cells were collected at different days after the start of differentiation, and the transcripts analysed for
expression levels of markers of adipocyte differentiation such as AP2, PPARy, CEB P(x, and FAS. Dkk- 1
treatment did not alter levels of FAS and AP2; however, PPARylevels were about 2-fold reduced in Dkk-1-
treated cells and C/EBPoc levels. . .
. . .
adipose tissue mass and are up-regulated by
Akt (Barthel et al., Endocrinolo -3562 (1997)). The reduced levels of circulating leptin in dkk-1
138: 3559
48
transgenic animals could be a direct effect of decreased adipose mass and/or decreased Akt activity in
adipose tissue, without being limited. . .

A significant reduction in the levels of secreted insulin was observed herein following 8 days of
Dkk-1 injection, and smaller effects in transgenic
animals overexpressing dkk-1 in the muscle. Without being

limited to any one theory, the stronger effects in injected animals could be a result of. . . there may be smaller differences in insulin levels either due to compensatory mechanisms or due to a more localized effect of Dkk-1 in the muscle. Since Akt is known to stimulate islet cell proliferation and insulin production, and since the data herein show for the first time that Dkk-1-injected and transgenic mice have lower insulin levels, an antagonist to Dkk- 1 is now found useful in treating hypoinsulinemia, and conversely, Dkk- I itself is found useful in treating hyperinsulinemia.

. . .

in L6 muscle cells as well as in transgenic mice overexpressin cr the protein in muscle. Treatment of muscle cells with Dkk-1 resulted in a decrease in the basal and insulin-stimulated glucose uptake. This effect was observed following both short-term and long-term treatment,

49

suggesting, without being limited to any one theory, that Dkk-1 may affect both the activity as well as the expression levels of proteins in the insulin signaling pathway. Consistent with this. . .

. . .

obesity and hyperinsulinernia, as well as being useful as a diagnostic marker in assays for such conditions. Also, an antagonist to Dkk-1 is expected to inhibit the progression of the diabetes phenotype in transgenic animal models disclosed in U.S. Pat. No. 6,187,991.

Example 2

Development of Anti-Dkk-1 Monoclonal Antibodies

Five female Balb/c mice (Charles River Laboratories, Wilmington, DE) were hyperimmunized with purified recombinant polyhistidine-tagged (HIS8) human Dkk- I expressed. . . used for each animal, administered via footpad. After five injections, B-cells from the lymph nodes of the five mice, demonstrating high anti-Dkk- 1 antibody titers, were fused with mouse myeloma cells (X63.Ag8.653; American Type Culture Collection, Manassas, VA) using the protocols described in Kohler and Milstein, supra, and Hongo et al.,. . .

All the seven antibody preparations bound Dkk-1 in Western immunoblots.

L6 cells were differentiated and treated for 48 hours in the absence of Dkk-1 (control) or in the presence of 40 nM Dkk-1 (plus or minus anti-Dkk-1 antibody 1G1.2D12.2D1 1 (ATCC No. PTA-3086) in an amount of 0.5 ttg/mL). Basal and insulin-stimulated glucose uptake in the L6 cells. . . .

50

Designation	ATQC Dep. No.	Deposit Date
DKKI.MAB3139,8CI 1.2GI 1. IDI	PTA-3084	February 21, 2001
DKK1.MAB3143.4C7.2HI0.2GI	PTA-3085	February 21, 2001
DKKLMAB3142. I G1.21) 12.2131 1	PTA-3086	February 21, 2001
DKK1..MAB3141.5B12.2C5.2A5	PTA-3087	February 21, 2001
DKKLMAB313 8.7C 1 1 16.2AS	PTA-3088	February 21, 2001
DKK1.MAB3140.7B2.2A6.2H4	PTA-3089	February 21, 2001
DKK1.MAB3144.5A2.2A8.1C3	PTA-3097	February 21, 2001

This deposit was made under the provisions of the Budapest Treaty on the International Recognition

of the Deposit. . . .

CLMEN. . . insulin resistance or hypoinsulinemia in marnmals comprising administering to a
mammal in need thereof an effective amount of an antagonist to Dickkopf- 1 (Dkk- 1).

4 The method of claim 1 wherein the antacronist is an antibody that binds Dkk- 1.
5 . The method of claim 4 wherein the antibody is a monoclonal antibody.
. . .
presence or onset of insulin resistance or hypoinsulinernia in a mammal comprising the steps of:
(a) measuring the amount of Dickkopf- I (Dkk- 1) in
a sample from said mammal; and
(b) comparing the amount determined in step (a) to an amount of Dkk- I.
. .

12 The method of claim I I wherein the anti-Dkk- 1
antibody comprises a label.

16 The method of claim IO wherein the mammal is human and human Dkk- 1 is being measured.

17 A kit for treating insulin resistance or hypoinsulinemia, said kit comprising:
(a) a container comprising an antagonist to Dkk-1;
and
(b) instructions for using the antagonist to treat insulin resistance or hypoinsulinernia.

18 The kit of claim 17 wherein the antagonist is an antibody that binds Dkk- 1

20 The kit of claim 18 wherein the antibody binds human Dkk-
1.

26 A method of treating obesity or hyperinsulinemia in mammals comprising administering to a mammal in
need thereof an effective amount of Dickkopf-I (Dkk-1
).
. . .
for detecting the presence or onset of obesity or hyperinsulinemia in a mammal comprising the
steps of.
(a) measuring the amount of Dickkopf-1 (Dkk]1) in a
sample from said mammal; and
(b) comparing the amount determined in step (a) to an amount of Dkk-l present in a standard sample, a
decreased level in the amount of Dkk-1 in step (a)
being indicative of obesity or hyperinsulinemia.

36 A kit for treating obesity or hyperinsulinemia, said kit comprising:
(a) a container comprising Dkk- 1; and
(b) instructions for using the Dkk- I to treat obesity or hyperinsulinemia.
. . .
the presence or onset of insulin resistance, hyperinsulinemia, hypoinsulinemia, or obesity, said kit comprising:
(a) a container comprising an antibody that binds Dickkopf-
1 (Dkk-1);
(b) a container comprising a standard sample containing Dkk-
1; and
(c) instructions for using the antibody and standard sample to detect insulin resistance,

hyperinsulinemia, hypoinsulinemia, or obesity, wherein either the antibody. . .

41 The kit of claim 39 wherein the Dkk-l is human Dkk-1 and the kit is for detecting non-insulin dependent diabetes or obesity.
53
. A method for repairing or regeneratingmusele in a mammal comprising. . .

47 A monoclonal antibody preparation prepared by hyperimmunizing mice with tagged Dkk-1 diluted in an adjuvant, fusing B-cells from the mice having anti-Dkk-I antibody titers with mouse myeloma cells and obtaining supernatants, harvesting the supernatants, screening the harvested supernatants for antibody production, injecting positive clones showing the highest immunobinding after. . .

=> d his

(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

L1	3942	S	WNT
L2	244	S	L1 (S) ANTAGON?
L3	553450	S	OSTEO? OR BONE
L4	70	S	L3 AND L2
L5	22597	S	MULTIPLE MYELOMA
L6	1	S	L5 AND L4
L7	1	S	L2 AND L5
L8	31029	S	MYELOMA
L9	1	S	L8 AND L2
L10	451	S	L1 AND L3
L11	7	S	L10 AND L5
L12	1	S	L11 NOT PY>2002
L13	70	S	(DICKKOPF () 1) OR (DKK () 1)
L14	2	S	L13 AND L11
L15	19	S	L13 AND L3
L16	14	S	L15 AND EXPRESS?
L17	6	S	L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005

L18	4365	S	WNT
L19	273	S	L1 (S) ANTAGON?
L20	273	S	L18 (S) ANTAGON?
L21	16913	S	MYELOMA
L22	5	S	L20 AND L21
L23	123	S	(DICKKOPF () 1) OR (DKK () 1)
L24	155	S	DICKKOPF-1 OR DKK1
L25	170	S	L23 OR L24
L26	61795	S	OSTEO?
L27	32	S	L26 AND L25
L28	7	S	L27 AND L21

FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005

L29	1307	S	WNT
L30	161	S	L29 (S) ANTAG?
L31	46	S	(DICKKOPF () 1) OR (DKK () 1)
L32	62	S	DICKKOPF-1 OR DKK1 OR DKK-1
L33	62	S	L32 OR L31
L34	27031	S	OSTEO?
L35	59451	S	L34 OR BONE
L36	87552	S	CANCER? OR TUMOR? OR NEOPLAS?

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L37        14570 S MYELOMA
L38           39 S L33 AND L34
L39           18 S L38 AND L37
L40            8 S L39 NOT PY>2002
L41           10 S L33/CLM
L42            1 S L41 AND L40
L43            4 S L33/AB
L44            1 S L42 AND L35

=> s d ibib
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L45           0 D IBIB
                (D(W)IBIB)

=> d l44 ibib

L44    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2002066509 PCTFULL  ED 20020910  EW 200235
TITLE (ENGLISH):         TREATMENT INVOLVING DKK-1 OR
                         ANTAGONISTS THEREOF
TITLE (FRENCH):          TRAITEMENT FAISANT APPEL A DKK-1 OU
                         AUX ANTAGONISTES DE DKK-1
INVENTOR(S):             DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116,
                         San Mateo, CA 94403, US;
                         STEWART, Timothy A., 465 Douglas Street, San Francisco,
                         CA 94114, US
PATENT ASSIGNEE(S):      GENENTECH, INC., 1 DNA Way, South San Francisco, CA
                         94080, US [US, US]
AGENT:                   HASAK, Janet E.$, GENENTECH, INC., MS 49, 1 DNA Way,
                         South San Francisco, CA 94080-4990$, US
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2002066509        A2 20020829
DESIGNATED STATES
       W:                AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
                         CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                         IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
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       RW (EAPO):        AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):         AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
                         TR
       RW (OAPI):        BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:       WO 2002-US4573       A  20020215
PRIORITY INFO.:          US 2001-60/269,435      20010216


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COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              16.18      62.30

FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
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```
=> s dickkopf-1 or DKK1 or DKK-1
             2 DICKKOPF
             1 DICKKOPFS
             3 DICKKOPF
               (DICKKOPF OR DICKKOPFS)
        354082 1
             2 DICKKOPF-1
               (DICKKOPF(W)1)
             2 DKK1
             3 DKK
             1 DKKS
             3 DKK
               (DKK OR DKKS)
        354082 1
             2 DKK-1
               (DKK(W)1)
L46          4 DICKKOPF-1 OR DKK1 OR DKK-1

=> s osteo?
L47       3245 OSTEO?

=> s l47 and l46
L48          0 L47 AND L46

=> s l46 and myeloma
           547 MYELOMA
            32 MYELOMAS
           567 MYELOMA
               (MYELOMA OR MYELOMAS)
L49          0 L46 AND MYELOMA

=> d his

     (FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005
L1         3942 S WNT
L2          244 S L1 (S) ANTAGON?
L3       553450 S OSTEO? OR BONE
L4           70 S L3 AND L2
L5        22597 S MULTIPLE MYELOMA
L6            1 S L5 AND L4
L7            1 S L2 AND L5
L8        31029 S MYELOMA
L9            1 S L8 AND L2
L10         451 S L1 AND L3
L11           7 S L10 AND L5
L12           1 S L11 NOT PY>2002
L13          70 S (DICKKOPF () 1) OR (DKK () 1)
L14           2 S L13 AND L11
L15          19 S L13 AND L3
L16          14 S L15 AND EXPRESS?
L17           6 S L16 NOT PY>2002

     FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005
L18        4365 S WNT
L19         273 S L1 (S) ANTAGON?
L20         273 S L18 (S) ANTAGON?
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L21        16913 S MYELOMA
L22            5 S L20 AND L21
L23          123 S (DICKKOPF () 1) OR (DKK () 1)
L24          155 S DICKKOPF-1 OR DKK1
L25          170 S L23 OR L24
L26        61795 S OSTEO?
L27           32 S L26 AND L25
L28            7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29         1307 S WNT
L30          161 S L29 (S) ANTAG?
L31           46 S (DICKKOPF () 1) OR (DKK () 1)
L32           62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33           62 S L32 OR L31
L34        27031 S OSTEO?
L35        59451 S L34 OR BONE
L36        87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37        14570 S MYELOMA
L38           39 S L33 AND L34
L39           18 S L38 AND L37
L40            8 S L39 NOT PY>2002
L41           10 S L33/CLM
L42            1 S L41 AND L40
L43            4 S L33/AB
L44            1 S L42 AND L35
L45            0 S D IBIB

     FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
L46            4 S DICKKOPF-1 OR DKK1 OR DKK-1
L47         3245 S OSTEO?
L48            0 S L47 AND L46
L49            0 S L46 AND MYELOMA

=> file pctfull
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   0.82      63.12

FILE 'PCTFULL' ENTERED AT 13:17:23 ON 25 JUL 2005
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FILE LAST UPDATED:         19 JUL 2005      <20050719/UP>
MOST RECENT UPDATE WEEK:       200528        <200528/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s l43 and l35
L50            4 L43 AND L35

=> d ibib 1-4

L50    ANSWER 1 OF 4     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2005049640 PCTFULL  ED 20050607  EW 200522
TITLE (ENGLISH):         RHESUS MONKEY DICKKOPF-1, NUCLEOTIDES ENCODING SAME,
                         AND USES THEREOF
TITLE (FRENCH):          PROTEINE DICKKOPF-1 DE SINGE RHESUS, NUCLEOTIDES CODANT
                         LADITE PROTEINE, ET PROCEDES D'UTILISATION
INVENTOR(S):             HARADA, Shun-ichi, 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907, US [JP, US];
                         KASPARCOVA, Viera, 126 East Lincoln Avenue, Rahway, NJ
                         07065-0907, US [CZ, US];
                         GLANTSCHNIG, Helmut, 126 East Lincoln Avenue, Rahway,
                         NJ 07065-0907, US [AT, US]
```

PATENT ASSIGNEE(S): MERCK & CO., INC., 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [US, US], for all designates States except US;
HARADA, Shun-ichi, 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [JP, US], for US only;
KASPARCOVA, Viera, 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [CZ, US], for US only;
GLANTSCHNIG, Helmut, 126 East Lincoln Avenue, Rahway, NJ 07065-0907, US [AT, US], for US only

AGENT: MERCK & CO., INC.$, 126 East Lincoln Avenue, Rahway, NJ 07065-0907$, US

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005049640	A2	20050602

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW
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RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LU MC NL PL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2004-US38489 A 20041112
PRIORITY INFO.: US 2003-60/520,708 20031117

L50 ANSWER 2 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2004053063 PCTFULL ED 20040630 EW 200426
TITLE (ENGLISH): MOLECULAR DETERMINANTS OF MYELOMA BONE DISEASE AND USES THEREOF
TITLE (FRENCH): DETERMINANTS MOLECULAIRES DE MALADIE OSSEUSE DE TYPE MYELOME ET UTILISATIONS DE CEUX-CI
INVENTOR(S): SHAUGHNESSY, John, D., 4317 Old Oak Drive, Little Rock, AR 72222, US
PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ARKANSAS, 2404 North University Avenue, Little Rock, AR 72207-3608, US [US, US]
AGENT: ADLER, Benjamin, A.$, Adler & Associates, 8011 Candle Lane, Houston, TX 77071$, US

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004053063	A2	20040624

DESIGNATED STATES
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2003-US38372 A 20031204
PRIORITY INFO.: US 2002-60/431,040 20021205

L50 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002092015 PCTFULL ED 20021210 EW 200247
TITLE (ENGLISH): REAGENTS AND METHODS FOR MODULATING DKK-MEDIATED INTERACTIONS
TITLE (FRENCH): REACTIFS ET PROCEDES DESTINES A MODULER DES INTERACTIONS INDUITES PAR DKK
INVENTOR(S): ALLEN, Kristina, 11 Oliver Lane, Hopkinton, MA 01748-3108, US [US, US];
ANISOWICZ, Anthony, 50 Upham Street, West Newton, MA 02465, US [US, US];
BHAT, Bheem, M., 1214 Mayapple Lane, West Chester, PA 19380, US [IN, US];
DAMAGNEZ, Veronique, 125 Water Street, Framingham, MA 01701, US [FR, US];
ROBINSON, John, Allen, 23 Webb Road, Downingtown, PA 19335, US [US, US];
YAWORSKY, Paul, J., 13 Hobart Lane, Rockland, MA 02370, US [US, US]
PATENT ASSIGNEE(S): GENOME THERAPEUTICS CORPORATION, 100 Beaver Street, Waltham, MA 02453, US [US, US], for all designates States except US;
WYETH, Five Giralda Farms, Madison, NJ 07928, US [US, US], for all designates States except US;
ALLEN, Kristina, 11 Oliver Lane, Hopkinton, MA 01748-3108, US [US, US], for US only;
ANISOWICZ, Anthony, 50 Upham Street, West Newton, MA 02465, US [US, US], for US only;
BHAT, Bheem, M., 1214 Mayapple Lane, West Chester, PA 19380, US [IN, US], for US only;
DAMAGNEZ, Veronique, 125 Water Street, Framingham, MA 01701, US [FR, US], for US only;
ROBINSON, John, Allen, 23 Webb Road, Downingtown, PA 19335, US [US, US], for US only;
YAWORSKY, Paul, J., 13 Hobart Lane, Rockland, MA 02370, US [US, US], for US only
AGENT: REA, Teresa, Stanek$, Burns, Doane, Swecker & Mathis L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002092015	A2	20021121

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
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RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-US15982 A 20020517
PRIORITY INFO.: US 2001-60/291,311 20010517
US 2002-60/353,058 20020201
US 2002-60/361,293 20020304

L50 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2002066509 PCTFULL ED 20020910 EW 200235
TITLE (ENGLISH): TREATMENT INVOLVING DKK-1 OR ANTAGONISTS THEREOF
TITLE (FRENCH): TRAITEMENT FAISANT APPEL A DKK-1 OU AUX ANTAGONISTES DE

DKK-1

INVENTOR(S): DeALMEIDA, Venita I., 3014 Los Prados Avenue, #A116, San Mateo, CA 94403, US;
STEWART, Timothy A., 465 Douglas Street, San Francisco, CA 94114, US

PATENT ASSIGNEE(S): GENENTECH, INC., 1 DNA Way, South San Francisco, CA 94080, US [US, US]

AGENT: HASAK, Janet E.$, GENENTECH, INC., MS 49, 1 DNA Way, South San Francisco, CA 94080-4990$, US

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002066509	A2	20020829

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-US4573 A 20020215

PRIORITY INFO.: US 2001-60/269,435 20010216

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(FILE 'HOME' ENTERED AT 13:01:12 ON 25 JUL 2005)

FILE 'MEDLINE' ENTERED AT 13:01:25 ON 25 JUL 2005

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L2	244	S	L1 (S) ANTAGON?
L3	553450	S	OSTEO? OR BONE
L4	70	S	L3 AND L2
L5	22597	S	MULTIPLE MYELOMA
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L12	1	S	L11 NOT PY>2002
L13	70	S	(DICKKOPF () 1) OR (DKK () 1)
L14	2	S	L13 AND L11
L15	19	S	L13 AND L3
L16	14	S	L15 AND EXPRESS?
L17	6	S	L16 NOT PY>2002

FILE 'CAPLUS' ENTERED AT 13:06:53 ON 25 JUL 2005

L18	4365	S	WNT
L19	273	S	L1 (S) ANTAGON?
L20	273	S	L18 (S) ANTAGON?
L21	16913	S	MYELOMA
L22	5	S	L20 AND L21
L23	123	S	(DICKKOPF () 1) OR (DKK () 1)
L24	155	S	DICKKOPF-1 OR DKK1
L25	170	S	L23 OR L24
L26	61795	S	OSTEO?
L27	32	S	L26 AND L25

```
L28           7 S L27 AND L21

     FILE 'PCTFULL' ENTERED AT 13:10:21 ON 25 JUL 2005
L29        1307 S WNT
L30         161 S L29 (S) ANTAG?
L31          46 S (DICKKOPF () 1) OR (DKK () 1)
L32          62 S DICKKOPF-1 OR DKK1 OR DKK-1
L33          62 S L32 OR L31
L34       27031 S OSTEO?
L35       59451 S L34 OR BONE
L36       87552 S CANCER? OR TUMOR? OR NEOPLAS?
L37       14570 S MYELOMA
L38          39 S L33 AND L34
L39          18 S L38 AND L37
L40           8 S L39 NOT PY>2002
L41          10 S L33/CLM
L42           1 S L41 AND L40
L43           4 S L33/AB
L44           1 S L42 AND L35
L45           0 S D IBIB

     FILE 'DISSABS' ENTERED AT 13:16:14 ON 25 JUL 2005
L46           4 S DICKKOPF-1 OR DKK1 OR DKK-1
L47        3245 S OSTEO?
L48           0 S L47 AND L46
L49           0 S L46 AND MYELOMA

     FILE 'PCTFULL' ENTERED AT 13:17:23 ON 25 JUL 2005
L50           4 S L43 AND L35

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY    SESSION
FULL ESTIMATED COST                            5.34      68.46

STN INTERNATIONAL LOGOFF AT 13:18:35 ON 25 JUL 2005


Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *
```

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NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
NEWS  2          "Ask CAS" for self-help around the clock
NEWS  3  FEB 28  PATDPAFULL - New display fields provide for legal status
                 data from INPADOC
NEWS  4  FEB 28  BABS - Current-awareness alerts (SDIs) available
NEWS  5  MAR 02  GBFULL: New full-text patent database on STN
NEWS  6  MAR 03  REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
NEWS  8  MAR 22  KOREAPAT now updated monthly; patent information enhanced
NEWS  9  MAR 22  Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS  10 MAR 22  PATDPASPC - New patent database available
NEWS  11 MAR 22  REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS  12 APR 04  EPFULL enhanced with additional patent information and new
                 fields
NEWS  13 APR 04  EMBASE - Database reloaded and enhanced
NEWS  14 APR 18  New CAS Information Use Policies available online
NEWS  15 APR 25  Patent searching, including current-awareness alerts (SDIs),
                 based on application date in CA/CAplus and USPATFULL/USPAT2
                 may be affected by a change in filing date for U.S.
                 applications.
NEWS  16 APR 28  Improved searching of U.S. Patent Classifications for
                 U.S. patent records in CA/CAplus
NEWS  17 MAY 23  GBFULL enhanced with patent drawing images
NEWS  18 MAY 23  REGISTRY has been enhanced with source information from
                 CHEMCATS
NEWS  19 JUN 06  The Analysis Edition of STN Express with Discover!
                 (Version 8.0 for Windows) now available
NEWS  20 JUN 13  RUSSIAPAT: New full-text patent database on STN
NEWS  21 JUN 13  FRFULL enhanced with patent drawing images
NEWS  22 JUN 27  MARPAT displays enhanced with expanded G-group definitions
                 and text labels
NEWS  23 JUL 01  MEDICONF removed from STN
NEWS  24 JUL 07  STN Patent Forums to be held in July 2005
NEWS  25 JUL 13  SCISEARCH reloaded
NEWS  26 JUL 20  Powerful new interactive analysis and visualization software,
                 STN AnaVist, now available

NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *


*ENCOMPPAT    - EnCompass Patent File 1964-present (Supporters)
*ENCOMPPAT2   - EnCompass Patent File 1964-Present (Non-Supporters)

  * The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005
```

```
=> file medline
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005

 FILE LAST UPDATED: 23 JUL 2005 (20050723/UP).  FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available.  For details enter HELP
 RLOAD at an arrow promt (=>).  See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s bone
        424243 BONE
         91740 BONES
L1      446342 BONE
                 (BONE OR BONES)

=> s (dickkopf () 1) or (dickkopf-1) or dickkopf1 or (dkk1) or (dkk-1) or (dkk () 1)
            85 DICKKOPF
             8 DICKKOPFS
            90 DICKKOPF
                 (DICKKOPF OR DICKKOPFS)
       3513889 1
            49 DICKKOPF (W) 1
            85 DICKKOPF
             8 DICKKOPFS
            90 DICKKOPF
                 (DICKKOPF OR DICKKOPFS)
       3513889 1
            49 DICKKOPF-1
                 (DICKKOPF(W)1)
            17 DICKKOPF1
           106 DKK1
           119 DKK
             9 DKKS
           121 DKK
                 (DKK OR DKKS)
       3513889 1
            44 DKK-1
                 (DKK(W)1)
           119 DKK
             9 DKKS
           121 DKK
                 (DKK OR DKKS)
       3513889 1
            44 DKK (W) 1
L2         133 (DICKKOPF (W) 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DKK-
               1) OR (DKK (W) 1)

=> s l2 and l1
```

```
L3          36 L2 AND L1

=> s l3 not py>2002
       1489868 PY>2002
L4          12 L3 NOT PY>2002

=> s l4 and express?
        932565 EXPRESS?
L5           9 L4 AND EXPRESS?

=> d ibib 1-4

L5   ANSWER 1 OF 9     MEDLINE on STN
ACCESSION NUMBER:   2002693855     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12455632
TITLE:              Bmp, Fgf and Wnt signalling in programmed cell death and
                    chondrogenesis during vertebrate limb development: the role
                    of Dickkopf-1.
AUTHOR:             Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE:   Institut fur Entwicklungs- und Molekularbiologie der Tiere
                    (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SOURCE:             International journal of developmental biology, (2002) 46
                    (7) 943-7.
                    Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY:       Spain
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200306
ENTRY DATE:         Entered STN: 20021214
                    Last Updated on STN: 20030619
                    Entered Medline: 20030618

L5   ANSWER 2 OF 9     MEDLINE on STN
ACCESSION NUMBER:   2002131765     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11867524
TITLE:              The Wnt antagonist Dickkopf-1 is
                    regulated by Bmp signaling and c-Jun and modulates
                    programmed cell death.
AUTHOR:             Grotewold Lars; Ruther Ulrich
CORPORATE SOURCE:   Entwicklungs- und Molekularbiologie der Tiere,
                    Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany..
                    lars.grotewold@uni-duesseldorf.de
SOURCE:             EMBO journal, (2002 Mar 1) 21 (5) 966-75.
                    Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200205
ENTRY DATE:         Entered STN: 20020228
                    Last Updated on STN: 20020515
                    Entered Medline: 20020514

L5   ANSWER 3 OF 9     MEDLINE on STN
ACCESSION NUMBER:   2001447406     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11291860
TITLE:              The role of the homeodomain protein Bozozok in zebrafish
                    axis formation.
AUTHOR:             Solnica-Krezel L; Driever W
CORPORATE SOURCE:   Department of Molecular Biology, Vanderbilt University,
                    Nashville, Tennessee 37235, USA.. lilianna.solnica-
                    krezel@vanderbilt.edu
SOURCE:             International journal of developmental biology, (2001) 45
                    (1) 299-310.
```

Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L5 ANSWER 4 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001447398 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291852
TITLE: Dickkopf1 and the Spemann-Mangold head organizer.
AUTHOR: Niehrs C; Kazanskaya O; Wu W; Glinka A
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Heidelberg, Germany.
SOURCE: International journal of developmental biology, (2001) 45 (1) 237-40. Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

=> d ibib 5-7

L5 ANSWER 5 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001168646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11269304
TITLE: Development. The path to the heart and the road not taken.
AUTHOR: Olson E N
CORPORATE SOURCE: Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.. eolson@hamon.swmed.edu
SOURCE: Science, (2001 Mar 23) 291 (5512) 2327-8.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20021218
Entered Medline: 20010412

L5 ANSWER 6 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in Xenopus laevis.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: RO1 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

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LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200103
ENTRY DATE:         Entered STN: 20010404
                    Last Updated on STN: 20010404
                    Entered Medline: 20010315

L5   ANSWER 7 OF 9     MEDLINE on STN
ACCESSION NUMBER:   2001069917     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11044411
TITLE:              The role of Xenopus dickkopf1 in prechordal plate
                    specification and neural patterning.
AUTHOR:             Kazanskaya O; Glinka A; Niehrs C
CORPORATE SOURCE:   Division of Molecular Embryology, Deutsches
                    Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120
                    Heidelberg, Germany.
SOURCE:             Development (Cambridge, England), (2000 Nov) 127 (22)
                    4981-92.
                    Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY:       ENGLAND: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200101
ENTRY DATE:         Entered STN: 20010322
                    Last Updated on STN: 20010322
                    Entered Medline: 20010104


=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1        446342 S BONE
L2           133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3            36 S L2 AND L1
L4            12 S L3 NOT PY>2002
L5             9 S L4 AND EXPRESS?

=> d ibib 8-9

L5   ANSWER 8 OF 9     MEDLINE on STN
ACCESSION NUMBER:   2000108581     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 10640703
TITLE:              Requirement for anti-dorsalizing morphogenetic protein in
                    organizer patterning.
AUTHOR:             Dosch R; Niehrs C
CORPORATE SOURCE:   Division of Molecular Embryology, Deutsches
                    Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120,
                    Heidelberg, Germany.
SOURCE:             Mechanisms of development, (2000 Feb) 90 (2) 195-203.
                    Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY:       Ireland
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200004
ENTRY DATE:         Entered STN: 20000505
                    Last Updated on STN: 20000505
                    Entered Medline: 20000427

L5   ANSWER 9 OF 9     MEDLINE on STN
ACCESSION NUMBER:   1999425169     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 10495270
```

TITLE: Dickkopf genes are co-ordinately expressed in mesodermal lineages.
AUTHOR: Monaghan A P; Kioschis P; Wu W; Zuniga A; Bock D; Poustka A; Delius H; Niehrs C
CORPORATE SOURCE: Division of Molecular Biology of the Cell I, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany.
SOURCE: Mechanisms of development, (1999 Sep) 87 (1-2) 45-56. Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ243963; GENBANK-AJ243964
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

=> d 1-4

L5 ANSWER 1 OF 9 MEDLINE on STN
AN 2002693855 MEDLINE
DN PubMed ID: 12455632
TI Bmp, Fgf and Wnt signalling in programmed cell death and chondrogenesis during vertebrate limb development: the role of Dickkopf-1.
AU Grotewold Lars; Ruther Ulrich
CS Institut fur Entwicklungs- und Molekularbiologie der Tiere (EMT), Heinrich-Heine-Universitat, Dusseldorf, Germany.
SO International journal of developmental biology, (2002) 46 (7) 943-7. Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20021214
Last Updated on STN: 20030619
Entered Medline: 20030618

L5 ANSWER 2 OF 9 MEDLINE on STN
AN 2002131765 MEDLINE
DN PubMed ID: 11867524
TI The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AU Grotewold Lars; Ruther Ulrich
CS Entwicklungs- und Molekularbiologie der Tiere, Heinrich-Heine Universitat, D-40225 Dusseldorf, Germany.. lars.grotewold@uni-duesseldorf.de
SO EMBO journal, (2002 Mar 1) 21 (5) 966-75. Journal code: 8208664. ISSN: 0261-4189.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200205
ED Entered STN: 20020228
Last Updated on STN: 20020515
Entered Medline: 20020514

L5 ANSWER 3 OF 9 MEDLINE on STN
AN 2001447406 MEDLINE
DN PubMed ID: 11291860
TI The role of the homeodomain protein Bozozok in zebrafish axis formation.

AU Solnica-Krezel L; Driever W
CS Department of Molecular Biology, Vanderbilt University, Nashville, Tennessee 37235, USA.. lilianna.solnica-krezel@vanderbilt.edu
SO International journal of developmental biology, (2001) 45 (1) 299-310. Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L5 ANSWER 4 OF 9 MEDLINE on STN
AN 2001447398 MEDLINE
DN PubMed ID: 11291852
TI Dickkopf1 and the Spemann-Mangold head organizer.
AU Niehrs C; Kazanskaya O; Wu W; Glinka A
CS Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Heidelberg, Germany.
SO International journal of developmental biology, (2001) 45 (1) 237-40. Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

=> d kwic 4

L5 ANSWER 4 OF 9 MEDLINE on STN
TI Dickkopf1 and the Spemann-Mangold head organizer.
AB . . . the Spemann-Mangold organizer may be mediated by secreted Wnt antagonists. Wnts are potent posteriorizing factors and antagonize the Spemann-Mangold organizer. Dickkopf1 (dkk1) encodes a secreted effector expressed in head organizing centers of Xenopus, mouse and zebrafish. It acts as a Wnt inhibitor and is able together with. . . anteriorizes both mesendoderm and neuroectoderm, promoting prechordal plate and forebrain fates. Injection of inhibitory antibodies leads to microcephaly and cyclopia. Dkk1 thus is an essential mediator of the vertebrate head organizer.
CT Animals
Body Patterning
Bone Morphogenetic Proteins: AI, antagonists & inhibitors
Embryonic Induction
Head: EM, embryology
Mice
*Organizers, Embryonic: PH, physiology
Proteins: GE, genetics
. . .
CN 0 (Bone Morphogenetic Proteins); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (dkk1 protein, Xenopus); 0 (wnt8b protein, zebrafish)

=> d kwic 2

L5 ANSWER 2 OF 9 MEDLINE on STN
TI The Wnt antagonist Dickkopf-1 is regulated by Bmp signaling and c-Jun and modulates programmed cell death.
AB Dickkopf-1 (Dkk-1) has been shown to be a potent inhibitor of Wnt/beta-catenin signaling in a variety of assays and organisms. In this study, we show that expression of Dkk-1 overlaps significantly with the sites of programmed cell death in normal as well as mutant vertebrate limb development, and identify several of its upstream regulators, one of which is Bmp-4. Interestingly, Bmp-4 only activates Dkk-1 when it concomitantly induces apoptosis. Moreover, Dkk-1 is heavily up-regulated by UV irradiation and several other genotoxic stimuli. We further show that normal expression of Dkk-1 is dependent on the Ap-1 family member c-Jun and that overexpression of Dkk-1 enhances Bmp-triggered apoptosis in the vertebrate limb. Taken together, our results provide evidence for an important role of Dkk-1-mediated inhibition of Wnt/beta-catenin signaling in response to different stress signals that all converge on the activation of c-Jun in vivo.
CT Animals
Apoptosis: GE, genetics
Apoptosis: PH, physiology
Bone Morphogenetic Proteins: AI, antagonists & inhibitors
Bone Morphogenetic Proteins: PD, pharmacology
*Bone Morphogenetic Proteins: PH, physiology
Chick Embryo
Cytoskeletal Proteins: AI, antagonists & inhibitors
DNA-Binding Proteins: BI, biosynthesis
DNA-Binding Proteins: GE, genetics
. . . Implants
Enzyme Inhibitors: PD, pharmacology
*Extremities: EM, embryology
Fibroblast Growth Factors: PD, pharmacology
Fibroblasts: DE, drug effects
Fibroblasts: ME, metabolism
Gene Expression Regulation, Developmental: DE, drug effects
*Gene Expression Regulation, Developmental: PH, physiology
Gene Expression Regulation, Developmental: RE, radiation effects
Mesoderm: ME, metabolism
Mice
Mice, Knockout
Morphogenesis
Protein Biosynthesis
Proteins: GE, genetics
Proteins: . . .
CN 0 (Bone Morphogenetic Proteins); 0 (Cytoskeletal Proteins); 0 (DNA-Binding Proteins); 0 (Drug Implants); 0 (Enzyme Inhibitors); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0. . . 0 (Recombinant Fusion Proteins); 0 (Trans-Activators); 0 (Transcription Factor AP-1); 0 (Transcription Factors); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (bone morphogenetic protein 4); 0 (dkk1 protein, Xenopus); 0 (hedgehog protein, vertebrate); 0 (lymphoid enhancer-binding factor 1); 0 (wnt8b protein, zebrafish)

=> d kwic 5

L5 ANSWER 5 OF 9 MEDLINE on STN
CT Animals
*Blood Cells
Bone Morphogenetic Proteins: ME, metabolism
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Central Nervous System: EM, embryology
Central Nervous System: ME, metabolism
Cytoskeletal Proteins: ME, metabolism

```
      Drosophila: EM, embryology
      Drosophila: ME, metabolism
     *Drosophila Proteins
     *Embryonic Induction
      Endoderm: PH, physiology
        Gene Expression Regulation, Developmental
      Glycogen Synthase Kinase 3
     *Heart: EM, embryology
      Hematopoiesis
      Insect Proteins: ME, metabolism
      Mesoderm: CY, cytology
      Mesoderm:. . .
CN    0 (Bone Morphogenetic Proteins); 0 (Cytoskeletal Proteins); 0
      (Drosophila Proteins); 0 (Insect Proteins); 0 (Proteins); 0
      (Trans-Activators); 0 (Transcription Factors); 0 (Wnt-3 protein); 0
      (Xenopus Proteins); 0 (crescent protein, Xenopus); 0 (dkk1
      protein, Xenopus); 0 (dpp protein, Drosophila); 0 (wnt8a protein,
      Zebrafish); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC
      2.7.1.37 (Glycogen Synthase.  .  .


=> s osteo?
L6      211167 OSTEO?

=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1       446342 S BONE
L2          133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3           36 S L2 AND L1
L4           12 S L3 NOT PY>2002
L5            9 S L4 AND EXPRESS?
L6       211167 S OSTEO?

=> s l2 and l6
L7           24 L2 AND L6

=> s l5 not py>2002
      1489868 PY>2002
L8            9 L5 NOT PY>2002

=> s l8 not py>2001
      2029769 PY>2001
L9            7 L8 NOT PY>2001

=> d ibib 1-4

L9   ANSWER 1 OF 7     MEDLINE on STN
ACCESSION NUMBER:    2001447406     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 11291860
TITLE:               The role of the homeodomain protein Bozozok in zebrafish
                     axis formation.
AUTHOR:              Solnica-Krezel L; Driever W
CORPORATE SOURCE:    Department of Molecular Biology, Vanderbilt University,
                     Nashville, Tennessee 37235, USA.. lilianna.solnica-
                     krezel@vanderbilt.edu
SOURCE:              International journal of developmental biology, (2001) 45
                     (1) 299-310.
                     Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY:        Spain
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
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ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L9 ANSWER 2 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001447398 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11291852
TITLE: Dickkopf1 and the Spemann-Mangold head organizer.
AUTHOR: Niehrs C; Kazanskaya O; Wu W; Glinka A
CORPORATE SOURCE: Division of Molecular Embryology, Deutsches Krebsforschungszentrum, Heidelberg, Germany.
SOURCE: International journal of developmental biology, (2001) 45 (1) 237-40. Ref: 34
Journal code: 8917470. ISSN: 0214-6282.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

L9 ANSWER 3 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001168646 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11269304
TITLE: Development. The path to the heart and the road not taken.
AUTHOR: Olson E N
CORPORATE SOURCE: Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.. eolson@hamon.swmed.edu
SOURCE: Science, (2001 Mar 23) 291 (5512) 2327-8.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20021218
Entered Medline: 20010412

L9 ANSWER 4 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001150174 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11159911
TITLE: Wnt antagonism initiates cardiogenesis in Xenopus laevis.
AUTHOR: Schneider V A; Mercola M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: RO1 HL59502 (NHLBI)
SOURCE: Genes & development, (2001 Feb 1) 15 (3) 304-15.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

```
=> d kwic 2

L9   ANSWER 2 OF 7     MEDLINE on STN
TI   Dickkopf1 and the Spemann-Mangold head organizer.
AB   . . . the Spemann-Mangold organizer may be mediated by secreted Wnt
     antagonists. Wnts are potent posteriorizing factors and antagonize the
     Spemann-Mangold organizer. Dickkopf1 (dkk1) encodes a
     secreted effector expressed in head organizing centers of
     Xenopus, mouse and zebrafish. It acts as a Wnt inhibitor and is able
     together with. . . anteriorizes both mesendoderm and neuroectoderm,
     promoting prechordal plate and forebrain fates. Injection of inhibitory
     antibodies leads to microcephaly and cyclopia. Dkk1 thus is an
     essential mediator of the vertebrate head organizer.
CT    Animals
      Body Patterning
        Bone Morphogenetic Proteins: AI, antagonists & inhibitors
      Embryonic Induction
      Head: EM, embryology
      Mice
     *Organizers, Embryonic: PH, physiology
      Proteins: GE, genetics
. . .
CN   0 (Bone Morphogenetic Proteins); 0 (Proteins); 0 (Proto-Oncogene
     Proteins); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (dkk1
     protein, Xenopus); 0 (wnt8b protein, zebrafish)


=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1       446342 S BONE
L2          133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3           36 S L2 AND L1
L4           12 S L3 NOT PY>2002
L5            9 S L4 AND EXPRESS?
L6       211167 S OSTEO?
L7           24 S L2 AND L6
L8            9 S L5 NOT PY>2002
L9            7 S L8 NOT PY>2001

=> s l7 not py>2001
      2029769 PY>2001
L10           0 L7 NOT PY>2001

=> s l7 not py>2002
      1489868 PY>2002
L11           3 L7 NOT PY>2002

=> d ibib 1-3

L11  ANSWER 1 OF 3     MEDLINE on STN
ACCESSION NUMBER:    2002280313     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 12021176
TITLE:               Global gene profiling in human endometrium during the
                     window of implantation.
AUTHOR:              Kao L C; Tulac S; Lobo S; Imani B; Yang J P; Germeyer A;
                     Osteen K; Taylor R N; Lessey B A; Giudice L C
CORPORATE SOURCE:    Department of Gynecology and Obstetrics, Stanford
                     University, Stanford, California 94305, USA.
CONTRACT NUMBER:     U54 HD31398 (NICHD)
SOURCE:              Endocrinology, (2002 Jun) 143 (6) 2119-38.
                     Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY:        United States
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DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020522
Last Updated on STN: 20020619
Entered Medline: 20020618

L11 ANSWER 2 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2002275003 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12015398
TITLE: Regulation of bone formation and vision by LRP5.
COMMENT: Comment on: N Engl J Med. 2002 May 16;346(20):1513-21. PubMed ID: 12015390
AUTHOR: Patel Millan S; Karsenty Gerard
SOURCE: New England journal of medicine, (2002 May 16) 346 (20) 1572-4.
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Space Life Sciences
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20020623
Entered Medline: 20020522

L11 ANSWER 3 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2002274995 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12015390
TITLE: High bone density due to a mutation in LDL-receptor-related protein 5.
COMMENT: Comment in: N Engl J Med. 2002 May 16;346(20):1572-4. PubMed ID: 12015398
Comment in: N Engl J Med. 2002 Sep 19;347(12):943-4; author reply 943-4. PubMed ID: 12239268
Comment in: N Engl J Med. 2002 Sep 19;347(12):943-4; author reply 943-4. PubMed ID: 12240686
Comment in: N Engl J Med. 2004 May 13;350(20):2096-9; author reply 2096-9. PubMed ID: 15141052
AUTHOR: Boyden Lynn M; Mao Junhao; Belsky Joseph; Mitzner Lyle; Farhi Anita; Mitnick Mary A; Wu Dianqing; Insogna Karl; Lifton Richard P
CORPORATE SOURCE: Department of Genetics, Yale University School of Medicine, New Haven, Connecticut 06510, USA.
CONTRACT NUMBER: AG15345 (NIA)
AR46032 (NIAMS)
CA85420 (NCI)
RR00125 (NCRR)
SOURCE: New England journal of medicine, (2002 May 16) 346 (20) 1513-21.
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20020926
Entered Medline: 20020522

=> d kwic 3

```
L11  ANSWER 3 OF 3     MEDLINE on STN
AB   BACKGROUND: Osteoporosis is a major public health problem of
     largely unknown cause.  Loss-of-function mutations in the gene for
     low-density lipoprotein receptor-related protein 5 (LRP5), which acts in
     the Wnt signaling pathway, have been shown to cause osteoporosis
     -pseudoglioma.  METHODS: We performed genetic and biochemical analyses of
     a kindred with an autosomal dominant syndrome characterized by high bone
     density,.  .  .  flies to humans.  Markers of bone resorption were normal
     in the affected subjects, whereas markers of bone formation such as
     osteocalcin were markedly elevated.  Levels of fibronectin, a
     known target of signaling by Wnt, a developmental protein, were also
     elevated.  In vitro studies showed that the normal inhibition of Wnt
     signaling by another protein, Dickkopf-1 (Dkk
     -1), was defective in the presence of LRP5V171 and that this
     resulted in increased signaling due to unopposed Wnt activity.
     CONCLUSIONS:.  .  .  LRP5 function in high bone mass and point to Dkk as a
     potential target for the prevention or treatment of osteoporosis
     .
CT   .  .  .
GE, genetics
      Case-Control Studies
      Chromosomes, Human, Pair 11
      Genes, Dominant
      Genotype
      Humans
      Mandible: PA, pathology
      Mandible: RA, radiography
      Mutation, Missense
        Osteogenesis: PH, physiology
      Palate: PA, pathology
      Pedigree
     *Point Mutation
      Proteins: PD, pharmacology
      Proto-Oncogene Proteins: AI, antagonists & inhibitors
     *Proto-Oncogene Proteins:.  .  .
CN   0 (Biological Markers); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0
     (Receptors, LDL); 0 (Wnt proteins); 0 (Zebrafish Proteins); 0 (
     dkk1 protein, Xenopus); 0 (lipoprotein receptor related protein
     5); 0 (wnt8b protein, zebrafish)


=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

     FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1        446342 S BONE
L2           133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3            36 S L2 AND L1
L4            12 S L3 NOT PY>2002
L5             9 S L4 AND EXPRESS?
L6        211167 S OSTEO?
L7            24 S L2 AND L6
L8             9 S L5 NOT PY>2002
L9             7 S L8 NOT PY>2001
L10            0 S L7 NOT PY>2001
L11            3 S L7 NOT PY>2002

=> s lesion
          141659 LESION
          302187 LESIONS
L12       391994 LESION
                 (LESION OR LESIONS)
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=> s l12 and l2
L13          5 L12 AND L2

=> s l13 not py>2002
       1489868 PY>2002
L14          0 L13 NOT PY>2002

=> d his

     (FILE 'HOME' ENTERED AT 16:15:45 ON 25 JUL 2005)

    FILE 'MEDLINE' ENTERED AT 16:16:12 ON 25 JUL 2005
L1        446342 S BONE
L2           133 S (DICKKOPF () 1) OR (DICKKOPF-1) OR DICKKOPF1 OR (DKK1) OR (DK
L3            36 S L2 AND L1
L4            12 S L3 NOT PY>2002
L5             9 S L4 AND EXPRESS?
L6        211167 S OSTEO?
L7            24 S L2 AND L6
L8             9 S L5 NOT PY>2002
L9             7 S L8 NOT PY>2001
L10            0 S L7 NOT PY>2001
L11            3 S L7 NOT PY>2002
L12       391994 S LESION
L13            5 S L12 AND L2
L14            0 S L13 NOT PY>2002

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                10.06      10.27

STN INTERNATIONAL LOGOFF AT 16:26:32 ON 25 JUL 2005
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